WHITE MATTER CONNECTIVITY DIFFERENCES BETWEEN SENSORIMOTOR REGIONS IN INDIVIDUALS WHO STUTTER

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Heterogeneity in neural activations and structural anomalies associated with stuttering have led researchers to postulate that stuttering is due to a network default. Widespread differences in white matter integrity surrounding areas involved in sensorimotor integration have been reported in people who stutter, but the connectivity between these regions has not been examined. This preliminary study examined white matter connectivity differences between sensorimotor areas involved in speech production in people who stutter when compared to those who do not stutter. White matter connectivity was assessed using Fractional Anisotropy (FA), Quantitative Anisotropy (QA), and white matter volume. Non-parametric analyses revealed significantly decreased white matter volume in tracts connecting the left Sylvian parietal temporal region (Spt) to both rolandic operculum (RO) and supramarginal gyrus (SMG) in people who stutter when compared to those who do not. Reduced FA in tracts connecting the left RO and premotor region (PM) was also associated with stuttering. Right hemisphere analysis revealed reduced white matter volume in the tract connecting the right Spt and Hechl's Gyrus (HG) in people who stutter when compared with those who do not. Correlational analyses showed a significant negative relationship between stuttering severity and QA of tracts connecting the left inferior frontal gyrus (IFG) to HG, and the IFG to SMG. QA of tracts connecting the right IFG to both the Spt and PM were also negatively correlated to stuttering severity scores. Scores assessing

impact of stuttering on a person's life had a negative correlation to QA of the left Spt -RO, and the right RO to both IFG and PM. Results of the study indicate that people who stutter showed reduced white matter volume and FA in tracts connecting sensorimotor areas and that the white matter integrity of some of the tracts were negatively correlated to stuttering severity.

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PREFACE

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Nomenclature

DIVA	**Directions In Velocities of Articulators**
dMRI	**Diffusion Magnetic Resonance Imaging**
DSI	**Diffusion Spectrum Imaging**
ODF	**Orientation Distribution Function**
FA	**Fractional Anisotropy**
HG	**Heschl's Gyrus**
HDFT	**High Definition Fiber Tracking**
HSFC	**Hierarchical State Feedback Control**
IFG	**Inferior Frontal Gyrus**
PM	**Premotor Cortex**
RO	**Rolandic Operculum**
Spt	**Sylvian parietal temporal area**
SMG	**Supramarginal Gyrus**
QA	**Quantitative Anisotropy**

1.0 INTRODUCTION

Speech production is a complex sensorimotor act that requires synergy between several processes involving the linguistic, cognitive, motor and sensory systems. Specifically, formulating language and successfully producing speech depends upon millisecond-level interactions and information transfer from various neural regions (Brainard & Doupe, 2002; Hickok, Houde, & Rong, 2011; Tourville & Guenther, 2011; Van der Merwe & McNeil, 2009). Evidence suggests that inconsistencies in the flow of information in these intricate networks due to anomalous neural function or structure are implicated in speech disruptions, such as those seen in people who stutter (Beal, Gracco, Lafaille, & Nil, 2007; Biermann-Ruben, Salmelin, & Schnitzler, 2005; Brown, Ingham, Ingham, Laird, & Fox, 2005; Cai et al., 2014; Chang & Zhu, 2013; Foundas, Bollich, et al., 2004; Watkins, Smith, Davis, & Howell, 2008). The development of stuttering has been attributed to a variety of neurological bases. These include abnormal cerebral dominance, atypical functioning of basal ganglia, mistiming of neural firing, and aberrant structural and functional connectivity between regions involved in speech production during speaking (Alm, 2007; Brown et al., 2005; Cai et al., 2014; Foundas, Bollich, et al., 2004; Travis, 1978). Aberrant activation patterns have been observed in people who stutter in sensorimotor regions that are engaged during speech production, such as supramarginal gyrus, superior temporal gyrus, rolandic operculum, primary motor and premotor regions, providing evidence for the neurological underpinnings of the disorder (Beal et al., 2007; Biermann-Ruben

et al., 2005; Brown et al., 2005; Foundas, Bollich, Corey, Hurley, & Heilman, 2001; Ingham et al., 2004; Neumann et al., 2005; Salmelin, Schnitzler, Schmitz, & Freund, 2000; Watkins et al., 2008).

Additional support for the role of sensorimotor dysfunction in stuttering comes from behavioral studies. For example, subtle auditory, somatosensory, and motor processing differences have been noted in people who stutter (De Nil & Abbs, 1991; Hulstijn, Summers, Van Lieshout, & Peters, 1992; Loucks & De Nil, 2006; Loucks & De Nil, 2012; Namasivayam & Van Lieshout, 2008; Zimmermann, 1980). Functional neuroimaging data point to a general trend of increased activation in the right motor and sensory (somatosensory and auditory) areas and decreased activation in the left auditory association areas in people who stutter when compared to people who do not stutter (Biermann-Ruben et al., 2005; Brown et al., 2005; Chang, Kenney, Loucks, Poletto, & Ludlow, 2009; De Nil et al., 2008; Foundas, Bollich, et al., 2004; Ingham et al., 2004; Salmelin et al., 1998). In addition, individuals who stutter show structural differences such as reduced asymmetry of the auditory areas and reduced white matter integrity surrounding sensorimotor regions involved in language formulation and speech production (Brown et al., 2005; Cai et al., 2014; Cieslak, Ingham, Ingham, & Grafton, 2015; Sommer, Koch, Paulus, Weiller, & Buchel, 2002). While atypical neural activation, reduced asymmetry, and decreased white matter integrity in sensorimotor areas have been reported in people who stutter, there is considerable variability across people who stutter and even within a person who stutters depending on the task that one is performing or the cognitive resources one uses (Brown et al., 2005; Cai et al., 2014). This heterogeneity in neural anomalies has led researchers to suggest that stuttering may not be due to a focal lesion or pathology but rather to a problem in the neural networks involved in speech production (Cai et al., 2014; Ludlow & Loucks, 2003).

Neuroanatomical variations (such as those seen in differing cortical morphology) are determined by a combination of intrinsic factors, such as gene expression, and extrinsic (environmental) factors, such as sensory information from the sensory nuclei in the thalamus (O'Leary & Sahara, 2008). The development of cortical morphology is primarily based on the generation and propagation of axons and selective pruning of redundant axons based on neural activity. An unstable speech production system might arise from lack of sufficient connections or failed pruning of redundant connections, resulting in inefficient transmission of time-sensitive information required for speaking (Ludlow, 1999). While reduced fractional anisotropy, a measure of white matter volume and myelination, has been noted surrounding sensorimotor areas involved in speech production, the connectivity between these areas has not been examined. It is critical to examine the connectivity between these areas to understand the link between reduced white matter integrity surrounding these areas and behavioral symptoms of stuttering.

This study aims to examine the structural connectivity between sensorimotor areas involved in speech production, namely the Sylvian parietal temporal area (Spt), Heschl's gyrus (HG), the premotor cortex (PM), the supramarginal gyrus (SMG), the inferior frontal gyrus (IFG) and the rolandic operculum (RO) The goal is to evaluate whether there are white matter connectivity differences between these regions in people who stutter as compared to people who do not stutter. Differences in connectivity patterns between sensorimotor regions involved in speech production combined with differences in functional activation patterns could provide an explanation for the widespread atypical activation and the lack of focal lesions associated with stuttering.

2.0 BACKGROUND AND RATIONALE

A potential neurological basis of stuttering was initially attributed to lack of cerebral dominance (Travis, 1931). Since then numerous researchers have attributed stuttering to abnormal functional activation, anomalous structural connectivity, and atypical lateralization of areas involved in speech production (Beal et al., 2007; Biermann-Ruben et al., 2005; Brown et al., 2005; Chang et al., 2009; Foundas et al., 2001; Foundas, Bollich, et al., 2004; Salmelin et al., 2000; Salmelin et al., 1998).

2.1 FUNCTIONAL ACTIVATION DIFFERENCES IN PEOPLE WHO STUTTER

Widespread atypical activation patterns have been noted in people who stutter during speech and non-speech tasks (Braun et al., 1997; Chang et al., 2009; De Nil, Kroll, & Houle, 2001; De Nil, Kroll, Kapur, & Houle, 2000; Fox et al., 2000; Ingham et al., 2004; Loucks, Kraft, Choo, Sharma, & Ambrose, 2011). Specifically, decreased activation patterns were noted in the left sensorimotor areas involved in speech production, namely the PM cortex, auditory regions, SMG, and RO. Increased activation in the right homolog of left hemisphere sensorimotor areas required for speech production was also reported (Brown et al., 2005; Chang et al., 2009; Ingham et al., 2004; Watkins et al., 2008).

2.1.1 Neural underpinnings of Auditory-Motor Integration in People Who Stutter

Possible neurological underpinnings of atypical auditory-motor integration in people who stutter have been investigated extensively (Beal et al., 2010; Chang et al., 2009; Civier, Tasko, & Guenther, 2010; Foundas, Bollich, et al., 2004; Foundas, Corey, Hurley, & Heilman, 2004; Salmelin et al., 1998). Chang et al. (2009) noted decreased activation in the left frontal regions, PM cortex, temperoparietal regions, and auditory areas, as well as increased activation patterns in the right superior temporal region, bilateral HG, and motor regions in people who stutter when compared to those who do not stutter. This activation pattern was seen during both speech and non-speech tasks, indicating differences in the level of recruitment of neural regions during oral movements not specific to speech.

Loucks et al. (2011) found similar patterns of reduced activation in the left PM cortex and temporoparietal regions in people who stutter during picture naming and phoneme monitoring tasks. These atypical activation patterns were also noted when people who stutter were fluent during choral reading tasks (Fox et al., 2000). In contrast, Watkins et al. (2008) reported decreased activation in the right auditory regions during a sentence production task under normal, delayed, or altered auditory feedback conditions when compared to people who did not stutter, even though both groups showed increased bilateral activation in right superior temporal cortex between delayed or altered feedback and normal feedback. However, their results confirmed previously noted decreased activation patterns in the left ventral PM regions and left HG during speech production, irrespective of speech fluency or auditory feedback conditions. The difference in findings can be attributed to the methodology used in the studies. The tasks were presented in pseudorandom order in the Watkins et al. study, leaving open the possibility of

crossover effects between conditions. In addition, the stimuli used in the Watkins et al. study were sentences; Loucks et al. used single words. Since stuttering increases with utterance length and complexity, it is possible that the regions recruited during speech production differed based on the complexity of the stimuli.

Evidence has also highlighted differences in the functional organization of bilateral auditory cortices between people who stutter and those who do not stutter (Salmelin et al., 1998). Sensitivity to the side of stimulation for each hemisphere was measured in a paradigm where short alternating tones were delivered to left and right ear during a fluency-enhancing task. People who stutter showed higher sensitivity to the side of stimulation in the right auditory cortex, whereas people who do not stutter show higher sensitivity to the side of stimulation in the left auditory cortex. Interestingly, the hemispheric balance was closest to that of fluent speakers when people who stutter were the most disfluent during an overt reading task. They concluded that the hemispheric balance is easily disturbed by an increase in complexity of utterances in people who stutter.

Studies investigating hemispheric laterality and binaural integration in people who stutter used dichotic listening tasks. Subgroups of ear advantage emerged depending on handedness and sex. Typically, people who do not stutter showed a right ear advantage in non-directed attention tasks. A subgroup of right-handed people who stutter exhibited right ear advantage similar to people who do not stutter. However, left-handed men who stutter exhibited left ear advantage for the same task. On the other hand, right-handed women who stutter showed a slight right ear advantage (Foundas, Bollich, et al., 2004).

Converging evidence suggests atypical auditory processing in people who stutter. The typically dominant activations in the left auditory areas seen in people who do not stutter are

decreased in people who stutter. The inter-hemispheric balance becomes unstable with increase in demand, such as with increases in syntactic or semantic complexity of the task. This is consistent with the hypothesis that stuttering could result from inefficient suppression of error maps in the feedback loop (Guenther, 2006; Max, Guenther, Gracco, Ghosh, & Wallace, 2004; Tourville & Guenther, 2011). Table 1 summarizes functional activation differences associated with stuttering.

Table 1: Functional activation differences between people who stutter and people who do not stutter

Functional Activation Differences in People who Stutter						
Study	Region	Right Hemisphere		Left Hemisphere		Stimuli/Task
Brown et al., 2005 Chang et al., 2009 Loucks et al., 2011 Salmelin et al., 2000	Inferior Frontal Region	Increased			Decreased Delayed	Review Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011). Overt Production of words (Salmelin et al., 2000)
Chang et al., 2009 Loucks et al., 2011 Watkins et al., 2008 Fox et al., 1996	Premotor	Increased			Decreased	Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011). Read sentences or a string of 'x' through prism glasses with delayed auditory feedback (Watkins et al., 2008).
Chang et al., 2009 Loucks et al., 2011	Temperoparietal region				Decreased	Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011).
Chang et al., 2009	Superior Temporal region	Increased			Decreased	Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011).

Table 1(Continued)

	Functional Activation Differences in People who Stutter					
Study	Region	Right Hemisphere		Left Hemisphere		Stimuli/Task
Watkins et al., 2008 Chang et al., 2009	Heschl's gyrus		Increased		Increased	Read sentences or a string of 'x' through prism glasses with delayed auditory feedback (Watkins et al., 2008).
Watkins et al., 2008 Salmelin et al., 2000 Bierman-Ruben et al., 2005	Rolandic operculum	Activated			Decreased Delayed	Read sentences or a string of 'x' through prism glasses with and without delayed auditory feedback (Watkins et al., 2008). Overt Production of words (Salmelin et al., 2000) Seen with sentence level task
Watkins et al., 2008 Chang et al., 2009 Loucks et al., 2011	Supramarginal gyrus		Decreased		Decreased	Read sentences or a string of 'x' through prism glasses with delayed auditory feedback (Watkins et al., 2008). Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011).
Brown et al 2005 Chang et al., 2009	Cerebellar	Increased				Review (Brown et al., 2005). Overt repetition of pseudo CVC words and non-speech stimuli (Chang et al., 2009). Phoneme identification and picture naming (Loucks et al., 2011).

2.1.2 Neural Underpinnings of Somatosensory-Motor Integration in People Who Stutter

Aberrant activation of regions involved in somatosensory-motor integration in people who stutter has been substantiated by several functional activation studies (Biermann-Ruben et al., 2005; Chang et al., 2009; Loucks et al., 2011; Watkins et al., 2008). Reduced functional neural activation has been reported in the left SMG (secondary somatosensory cortex) during both speech and non-speech tasks in individuals who stutter (Braun et al., 1997; Chang et al., 2009; Loucks et al., 2011). In addition to atypical activation of auditory areas, Watkins et al. (2008) also reported a bilateral reduction of activation in the sensorimotor cortex and right RO during a speaking task under normal, delayed, or altered auditory feedback conditions.

Temporal activation differences were also noted in the RO, an area that underlies the sensory representations of the articulators, in people who stutter (Brown et al., 2009; Sommer et al., 2002). Particularly, latencies of neural responses were seen in the left RO and inferior frontal gyrus during a listen-and-repeat task in people who stutter. In addition, activation was right lateralized in the RO for the words and sentence task in people who stutter instead of the left lateralization seen in fluent participants. There was no difference in activation between people who stutter and those who do not when listening to pure tones, suggesting that activation differences in language tasks cannot be attributed to auditory processing alone (Biermann-Ruben et al., 2005). These results were supported by PET studies that found higher rCBF in the right RO in people who stutter compared to people who do not stutter (Braun et al., 1997; Fox, Ingham, Ingham, Hirsch, & et al., 1996).

It is unclear if these atypical activations result in stuttering or are a result of compensatory strategies. Brown et al. (2005) hypothesized that the right lateralized activation associated with stuttering was due to the dysfunction of the left hemisphere and the over-activation of motor areas was due to lack of mastery of task. In other studies, fluency enhancing strategies such as choral reading eliminated atypical right lateralized over-activation in motor areas and reduced activation in right auditory regions, suggesting a compensatory role for the right hemisphere (Fox et al., 1996; Fox et al., 2000; Neumann et al., 2003). Regardless of whether the activation patterns associated with stuttering are the cause of stuttering or the result of compensatory skills, evidence indicates that people who stutter recruit neural circuits that are not typically recruited for speech production.

These consistent observations of atypical activation in auditory areas and motor areas have provided the basis for the assertion that stuttering may result from deficient sensorimotor integration. It also provides the rationale for the selection of regions for interest for this thesis.

2.1.3 Functional Activation Differences and Stuttering Severity

Very few functional activation studies have examined the link between surface stuttering behaviors and neural activation patterns. A negative correlation has been reported between the frequency of stuttering and activations of right superior regions, middle temporal regions, and frontal operculum (Fox et al., 2000; Preibisch et al., 2003). The correlation pattern between stuttering severity and activation of right hemisphere homolog of left hemisphere sensorimotor regions of speech production has led researchers to suggest that the increased right hemisphere activation associated with stuttering plays a compensatory role. The absence of increased

activation in the right hemisphere sensorimotor regions in children who stutter adds support to the assertion that the atypical right hemisphere activation seen in adults is compensatory (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008).

2.2 STRUCTURAL CONNECTIVITY DIFFERENCES OF SENSORIMOTOR NETWORK IN PEOPLE WHO STUTTER

Neuroanatomical differences have been associated with stuttering, especially surrounding speech-related sensorimotor areas. Reduced asymmetry of the planum temporale has been reported in people who stutter when compared to those who do not. The planum temporale, which is situated at the junction of the temporal and parietal cortex along the Sylvian fissure, consists of the auditory association areas involved in processing linguistic information (Foundas et al., 2001; Foundas, Bollich, et al., 2004). Cykowski et al (2008) found similar differences in the cortical folding of the planum temporale in people who stutter. In addition, an area deep in the planum temporale called the Sylvian parietal temporal (Spt) area has been reported to activate during sensorimotor tasks, and specifically during speech production (Hickok, Okada, & Serences, 2009). Considering the role of Spt in speech production and its location in the planum temporale, structural differences in the cortical folding of the planum temporale could contribute to the dysfunction in the sensorimotor integration during speaking in people who stutter.

In addition to hemispheric differences, reduced white matter integrity surrounding sensorimotor regions has been reported (Cai et al., 2014; Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Cieslak et al., 2015; Sommer et al., 2002; Watkins et al., 2008). A seminal work

by Sommer et al. (2002) revealed decreased white matter integrity surrounding the left RO and the SMG. These areas are functionally connected to the motor regions and are postulated to be involved in processing somatosensory input required for speech production. Widespread reduced fractional anisotropy (FA) of white matter fibers has also been reported in the right IFG, superior temporal gyrus, SMG, bilateral PM cortex, corpus callosum, arcuate fascicle, corticospinal tract, left angular gyrus, and cerebellar regions (Cai et al., 2014; Cieslak et al., 2015; Cykowski et al., 2008; Jäncke, Hänggi, & Steinmetz, 2004; Watkins et al., 2008). Refer to Table 2 for a summary of structural differences between people who stutter and those who do not. Reduced functional and structural connectivity between PM cortex and pars opercularis (BA 44) in the left hemisphere and increased connectivity between these areas in the right hemisphere was also noted in people who stutter (Chang et al., 2011). FA is an indirect measure of the white matter coherence based on the directional properties of water diffusion within a voxel. White matter refers to the myelin surrounding the axonal fibers connecting the cortical and sub-cortical regions and is involved in speed of information transfer. Decreased FA, which is associated with disorders such as Tourette syndrome (Jackson et al., 2011), might reflect myelin disruptions in the white matter tracts connecting cortical regions. Table 2 summarizes the structural differences between people who stutter and those who do not.

2.2.1 Neuroanatomical Differences and Stuttering Severity

Few studies have examined the correlation between stuttering severity and neuroanatomical differences in people who stutter. This paucity in evidence is possibly due to a key characteristic of stuttering: variability. Stuttering varies between situations depending on linguistic,

phonological and cognitive demands. As a result, the severity rating for a participant may not be a true representation of their stuttering disorder. An investigation linking behavioral symptoms of stuttering to neuroanatomical differences revealed negative correlation between stuttering severity and white matter connection between left mid-motor cortex and the ventral motor cortex (Cai et al., 2014). This finding is important, as the mid-motor cortex is located dorsally to the ventral motor cortex, an area that contains motor representations of the articulators.

Even though the etiology of the atypical neural activation patterns is unclear, it is evident that these atypical neural activation and structural anomalies in sensorimotor regions are present in varying degrees in people who stutter. This variability in neural anomalies have led to the hypothesis that stuttering is associated with deficient network connectivity rather than a problem in a focal region (Cai et al., 2014). Alternatively, since the heterogeneity in neural anomalies is only seen in the right hemisphere, it could be attributed to compensatory strategies. Most of the adult participants who stutter have stuttered since their childhood, and it is possible that they have developed strategies to manage their speech pattern. Even though decreased white matter connectivity and fractional anisotropy has been consistently noted in the left hemisphere regions involved in speech production such as rolandic operculum, arcuate fasciculus and cerebellum, the connectivity between these regions have not been mapped (Cieslak et al., 2015; Connally, Ward, Howell, & Watkins, 2014; Sommer et al., 2002; Watkins et al., 2008). It is therefore, important to examine the connectivity patterns between sensorimotor regions involved in speech to understand the loci of breakdown in people who stutter (Jäncke et al., 2004).

Table 2: Neural Structural Differences in People who stutter

Neural Structural Differences in People who Stutter			
Study	Region	Right Hemisphere	Left Hemisphere
Foundas et al.,2001 Jäncke et al., 2004	Planum Temporale	Larger	Larger
Foundas et al.,2001 Watkins et al., 2008 Chang et al., 2011	Frontal regions	No difference Decreased Fractional Anisotropy (FA)	No difference
Sommer et al., 2002	Rolandic Operculum		Reduced FA
Jäncke et al., 2004	Superior temporal gyrus	Increased white matter Volumes	
Jäncke et al., 2004	Inferior frontal gyrus	Increased white matter Volumes	
Jäncke et al., 2004	Primary motor	Increased white matter Volumes	
Watkins et al., 2008 Chang et al., 2011	Premotor regions	Decreased FA	
Watkins et al., 2008	Supramarginal gyrus	Increased FA	
Watkins et al., 2008	Cerebellum	Decreased FA	Decreased FA
Connally et al., 2014 Cieslak et al., 2015	Arcuate Fascicle	Decreased	Decreased

2.3 THEORIES OF SENSORIMOTOR DYSFUNCTION IN PEOPLE WHO STUTTER

Despite the widespread anatomical differences, a trend similar to the functional activation studies of reduced white matter integrity in the sensorimotor areas emerges. Evidence points to decreased connectivity surrounding left rolandic operculum, auditory cortices and premotor areas in people who stutter when compared to people who do not stutter. Reduced leftward asymmetry of the planum temporale is also associated with stuttering. These structural differences mirror functional activation differences noted in these regions. However, functional activation pattern differences in the right hemisphere do not follow the structural differences. For example, people who stutter exhibit decreased activation and increase FA in the right supramarginal gyrus. On the other hand, an increase in functional activation in right premotor and decrease in FA was seen in people who stutter when compared to people who do not stutter. Regardless of the inconsistency of the pattern of activation between the two groups, it is evident that sensorimotor areas such as rolandic operculum, supramarginal gyrus, planum temporale, superior temporal gyrus, inferior frontal gyrus and motor cortices are involved in speech production.

These findings support the hypothesis of several sensorimotor theories of speech production that asserts speech is a complex sensorimotor act (Guenther, 2006; Hickok et al., 2011; Tourville & Guenther, 2011; Van der Merwe & McNeil, 2009). For example, the Directions into Velocities of Articulators (DIVA) model suggests that the sensory information required for the motor target is predicted based on the expected motor output, gained through feedforward mechanisms (Golfinopoulos et al., 2011; Guenther, 2006; Tourville & Guenther, 2011; Tourville, Reilly, & Guenther, 2008). The model suggests that articulation requires an

interaction between the feedforward and feedback control systems. The feedback system consists of auditory and somatosensory feedback that is necessary for the continuous comparison of expected sensory information and the actual position of the articulators. Because speech is produced in milliseconds and it is inefficient to wait for sensory feedback for motor execution, therefore, the DIVA model incorporated a feedforward system to be the motor effector. The feedforward circuit transforms the temporal information of motor gestures required for speech into motor commands, which is then transmitted to the articulators for execution. Neural correlates were assigned to the components of the model based on neuroimaging studies. In the schematic depiction of DIVA model (figure 1), each box is a set of neurons depicting a neuronal representation. Arrows in the figure signify transformations from one neural representation to another.

According to the DIVA model, speech production begins with the activation of the Speech Sound Map cell of the corresponding sound produced. The Speech Sound Map contains representations of frequently used phonemes, similar to the 'mental syllabary' proposed by Levelt et al. (1999). The unit of speech sound represented in the Speech Sound Map could be phonemes or syllables. Therefore, in order to produce a syllable that is unfamiliar, phonemes that make up the syllable are produced sequentially. It is hypothesized that phonological encoding plays an important part in this process. The left ventral premotor area and posterior inferior frontal gyrus are proposed to be the neural correlates of the Speech Sound Map. They form a part of the feedforward system and project to the Articulatory Velocity and Position maps, which is represented in the primary motor cortex. Information from the Speech Sound Map cells is transformed into motor commands in the Articulatory Velocity and Position Maps. The model proposes an alternate pathway for feedforward commands from Speech Sound Map to the motor

cortex through the thalamus. Auditory and Somatosensory Target Maps also receive inputs from the Speech Sound Map cells so that the sensory expectation for a given sound can be encoded. During the babbling stage of speech acquisition, the Sensory (auditory and somatosensory) Target Maps are refined to encode sensory target range for the sound. The current auditory and somatosensory states are then compared to these targets through the feedback circuit.

The feedback circuit consists of both the sensory modalities: auditory and somatosensory. The Auditory State Map cells, which are postulated to be represented in posterior Heschl's Gyrus and anterior planum temporale represent the current acoustic state (Tourville et al., 2008). Any discrepancy in the matching of the current state to the target state is transmitted to the Auditory Error map cells. The Auditory Error Map, which is hypothesized to lie deep in the Sylvian fissure in the parietal temporal junction, is the inverse of the target map. Input to the target map is said to inhibit the expected sensory feedback for the target sound. This area is suggested to respond to both motor and sensory stimuli (Buchsbaum, Hickok, & Humphries, 2001; Hickok et al., 2009).

Similarly, neural correlates of Somatosensory State Maps are represented in the inferior parietal lobe. Any difference in the mapping of the current vocal tract state and the expected somatosensory sensation is transmitted to the motor cortex by the Somatosensory Error Map cells, which are represented in the supramarginal gyrus.

Evidence suggests that speech production recruits resources bilaterally (Ghosh, Tourville, & Guenther, 2008). Under normal auditory feedback conditions overt speech production is left lateralized but auditory feedback for error correction is right lateralized (Ghosh et al., 2008 2008). The feedforward and feedback systems are relevant for the investigation of the neural underpinnings of stuttering. The author further posits that the increased right hemisphere

activation could be the result of a weak feedforward control system in people who stutter. The evidence from this study substantiates Max et al., (2004) assertion that stuttering was the result of an overreliance on feedback system due to a weak or incorrect feedforward system. Widespread increased right hemisphere activation seen in people who stutter lends support to this hypothesis.

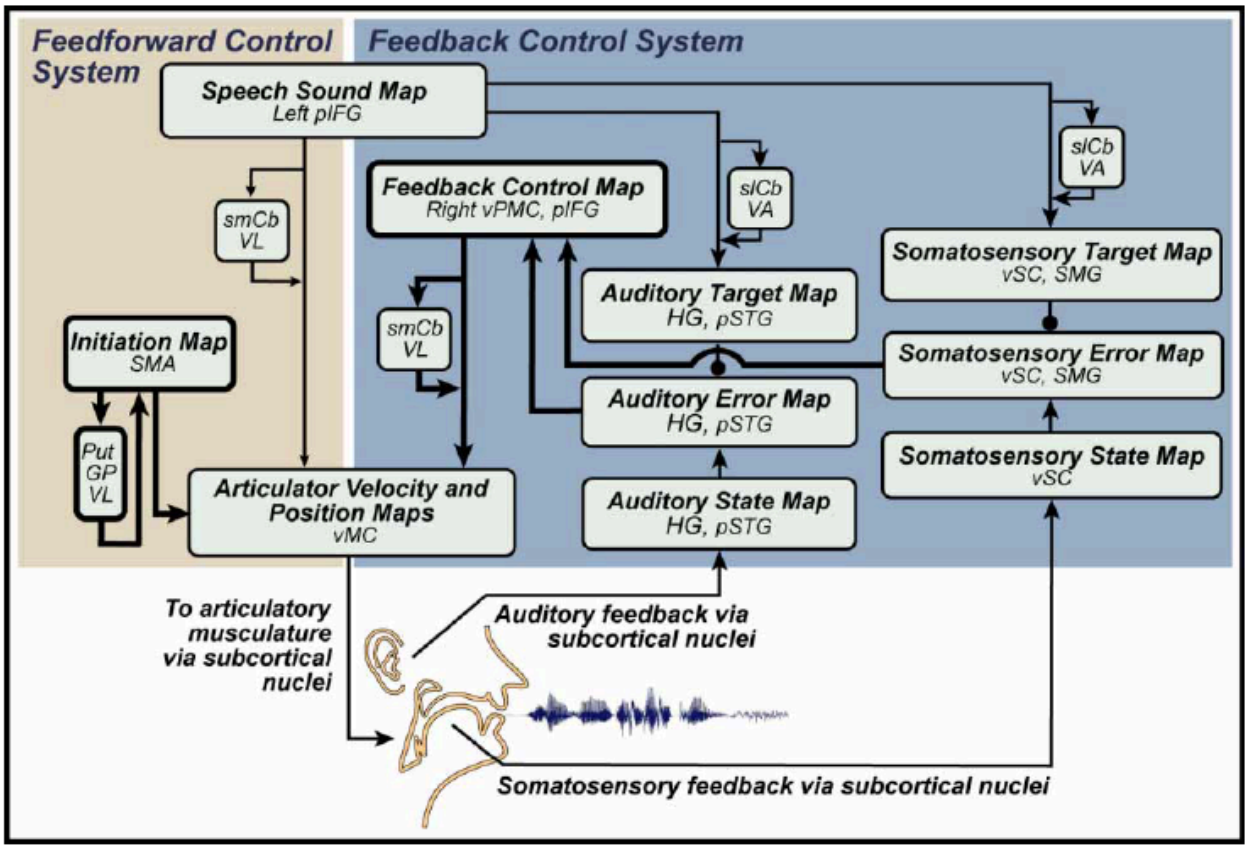


Figure 1: Depiction of DIVA Model of Speech Acquisition and Production with neural correlates

Note: HG: Heschl's Gyrus, pIFG: posterior inferior frontal gyrus, pSTG: posterior superior temporal gyrus, vMC: ventral motor cortex, vPMC: ventral premotor cortex, SMG: supramarginal gyrus, GP: globus pallidus, vSC: ventral somatosensory cortex, smCB: superior thalamus and slCB: superior lateral cerebellum (Tourville & Guenther, 2011)

Hickock et al. (2011), based on the Integrated State Feedback Model, postulated that the internal model of the vocal tract and the sensory feedback mechanism are accurate but the mapping between sensory and motor systems is noisy. A "noisy" translator results in incorrect predictions that will trigger incorrect error signal, which leads to repeated attempts to correct the error resulting in sound syllable repetitions (Hickok et al., 2011). However, the theory does not, by itself, explain blocks and prolongations experienced by people who stutter.

It has also been postulated by sensorimotor models of speech production such as DIVA and Hierarchical State Feedback Control model (HSFC) that there is an interaction between the two feedback systems: auditory and somatosensory (Hickok, 2012; Tourville & Guenther, 2011). HSFC hypothesizes that auditory targets represent higher-level linguistic units and somatosensory targets are lower-level phonemic units. Overt speech production activates both at the higher lexical level and the lower motor level. Behavioral evidence in support of this assertion points to a negative correlation between reliance on auditory and somatosensory feedback. This suggests a preference for one sensory modality over the other during speech production and that the preference is dependent on the context and type of speech sounds (Lametti, Nasir, & Ostry, 2012). For example planning for vowel production may be more reliant on auditory feedback while somatosensory feedback may be more important for consonant production, perhaps because consonant production involves constriction of the vocal tract (Feng, Gracco, & Max, 2011). The negative correlation between the auditory and somatosensory

reliance also opens the possibility of a gating mechanism that might inhibit one sensory modality in favor of another to make the sensorimotor integration process more efficient. Ghosh et al., (2010) found that both somatosensory and auditory goals are required for sibilant production. The interaction between the two sensory modalities is complex and differs based on the sounds produced.

Likewise, Van der Merwe & McNeil's (2009) framework posits that feedback and feedforward loops are involved in three out of the four phases of speech motor act (planning, programming and executing, but not linguistic symbolic phase), particularly for tasks such as adapting a core motor plan (co-articulation) and converting somatosensory instructions to muscle commands. Thus, these loops facilitate interactions between the sensory and motor systems, and these interactions are crucial for rapid and precise speech production. Any instabilities or dysfunction in these interactions are posited to result in stuttering (Alexander, Lee, Lazar, & Field, 2007; Hickok et al., 2011; Hickok et al., 2009; Max et al., 2004).

The foregoing theories and neuroimaging evidence indicate the importance of sensorimotor integration required for speech production and that a deficient process could lead to speech disruptions such as those seen in stuttering.

2.4 NEURAL CORRELATES OF SENSORIMOTOR NETWORK INVOLVED IN STUTTERING

A number of regions (Bohland & Guenther, 2006) are postulated to be involved in speech production including bilateral superior temporal cortex which encompasses HG, planum temporale and posterior temporal gyrus, somatosensory cortex, thalamus, insula, basal ganglia, motor, PM cortices and cerebellum. Several regions of interest have been identified as being important for sensory (auditory and somatosensory) feedback, motor planning, and sensorimotor integration required for speech production, namely HG, Spt PM, IFG, SMG, and RO. Regions of interest are depicted in Figure 1. Evidence for the involvement of these regions in sensorimotor integration during speech production comes from speech perception and productions models, (Hickok et al., 2011; Tourville & Guenther, 2011), functional neuroimaging studies (Beal et al., 2007; Brown, Ngan, & Liotti, 2008; Chang et al., 2008; Friederici, 2009; Hickok et al., 2011; Jürgens, 2002; Rauschecker, 2011; Tonkonogy & Goodglass, 1981; Vigneau et al., 2006) and structural connectivity studies (Fernández-Miranda et al., 2014; Fernandez-Miranda et al., 2012; Wang et al., 2013).

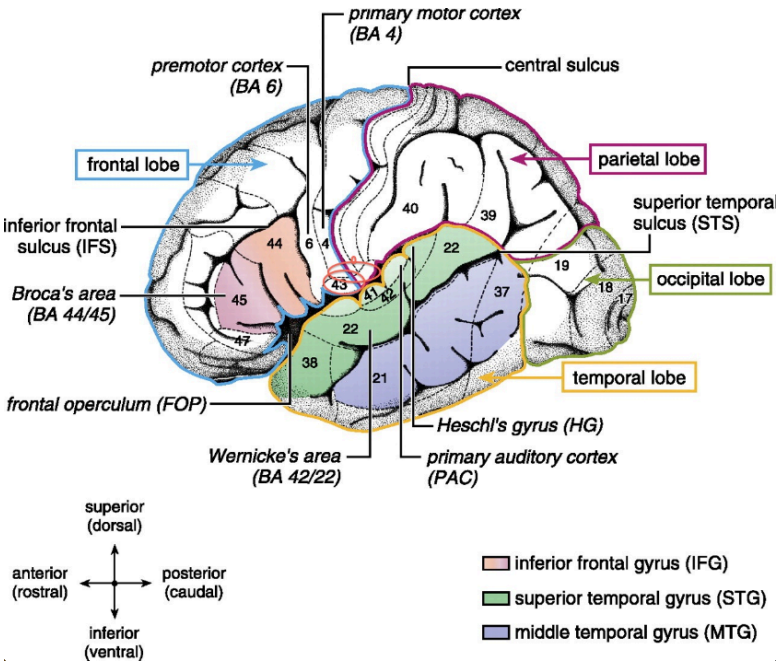


Figure 2: Illustration of lateral surface of left hemisphere

Note: Cortical parcellation of regions involved in speech production. The pink line denotes the central sulcus. Areas straddling the central sulcus are called sensorimotor cortices. The orange line denotes the Sylvian fissure. Area 43, together with the adjacent area in the ventral part of the sensorimotor cortex, is called the rolandic operculum (Friederici, 2011).

2.4.1 Regions of Interest

2.4.1.1 Premotor

PM, an area immediately anterior to the primary motor region, is postulated to translate motor programs and their temporal sequence to muscle movements required for speaking (Eickhoff, Heim, Zilles, & Amunts, 2009). It is said to be involved in achieving target output by converting expected output into specific muscle movements. Activation in the PM region has also been observed in silent listening conditions, so it is considered to be a component of the sensorimotor network (Hickok, Buchsbaum, Humphries, & Muftuler, 2003). Moreover, PM areas have also shown atypical activation in people who stutter compared to fluent peers. Since the PM cortex is hypothesized be the link between areas involved in phonological planning and sensorimotor integration (Golfinopoulos et al., 2011; Tourville & Guenther, 2011), any problem with connectivity of this area to sensory regions or frontal areas might result in a breakdown in the speech planning process.

2.4.1.2 Rolandic operculum

RO is an area that is situated in the ventral part of the precentral and postcentral cortex is said to underlie sensory representations of the speech articulators. RO activations has been associated with tongue movements and not lip movements (Brown et al., 2008). A meta-analysis of a cohort

of studies by Brown and colleagues showed that activations in the laryngeal area of the motor cortex were associated with phonation and activations in RO were associated with articulation. Neurons in RO were activated with the elevation and depression of the larynx as a whole (Brown et al., 2009). In addition, RO has been shown to activate during highly automated tasks such as syntactic processing during speech production (Indefrey et al., 2001).

Atypical activation patterns and reduced structural integrity of RO in individuals who stutter suggests differences in processing of sensorimotor integration required for speech (Braun et al., 1997; Brown et al., 2005; Salmelin et al., 2000; Sommer et al., 2002). Because RO activates during articulation and underlies the sensory representations of the articulators, it is an important part of the speech sensorimotor network.

2.4.1.3 Heschl's Gyrus

Several researchers have suggested that early cortical processing of speech perception involves auditory response areas, namely HG bilaterally, especially when people hear their own voice (Hickok, 2001; Rauschecker, 2011; Salmelin, 2007). Longer response latencies of auditory suppression neurons have also been reported in people who stutter during a passive listening task (Beal et al., 2010). In addition, studies have reported increased activation of HG bilaterally during speech production in people who stutter (Chang et al., 2009; Loucks et al., 2011). However, white matter connectivity of HG to motor planning and sensorimotor areas such as Spt, RO, and the SMG, has not yet been investigated. As HG plays a crucial role in the early processing of speech sounds, it is considered as a region of interest in the speech sensorimotor network.

2.4.1.4 Sylvian parietal temporal area

Projections from the primary auditory cortex (HG) bifurcate into a ventral stream and a dorsal stream. The dorsal stream, which is involved in mapping sound to representations of articulators, connects to the Spt, an area deep within the Sylvian fissure at the temporal-parietal junction. Functional imaging evidence suggests that Spt responds to both auditory and motor stimuli during speech production (Buchsbaum et al., 2001; Hickok et al., 2011; Hickok et al., 2009). Spt is postulated to be responsible for comparing the expected sensory (somatosensory and auditory) information to the expected motor output. However, activity in the Spt is greater for covert speech (subvocal rehearsal) than for continuous listening conditions, indicating a selectiveness for the motor modality specifically for laryngeal movement (Hickok, 2016; Hickok et al., 2011; Hickok et al., 2009). Furthermore, Spt is functionally connected to speech regions in the inferior frontal regions and the primary auditory area HG, suggesting Spt's role as a feedback mechanism in speech production (Hickok et al., 2011; Tourville et al., 2008). Finally, Spt is considered to be multi-sensory as it responds to both auditory and visual stimuli (Hickok et al., 2011; Hickok et al., 2009). Therefore, it has been postulated that Spt is involved in the auditory-motor integration of speech production (Brown et al., 2009; Hickok et al., 2011; Peschke, Ziegler, Kappes, & Baumgaertner, 2009; Tourville & Guenther, 2011).

Hickok et al. (2011) hypothesized that a noisy Spt is involved in stuttering, but the specific role of Spt in stuttering has not been investigated. Studies assessing structural connectivity differences have reported decreased white matter and gray matter integrity surrounding the left superior temporal gyrus and Sylvian fissure regions in individuals who stutter relative to those who do not (Beal et al., 2007; Jäncke et al., 2004). Since neurons in the

Spt activated for both motor and sensory stimuli during speech tasks, and because Spt is atypically activated in people who stutter, it is considered a crucial region in sensorimotor integration.

2.4.1.5 Supramarginal gyrus

SMG is part of the somatosensory association cortex and lies in the temporoparietal-occipital area. This area is associated with processing and elaborating sensory information from the primary sensory cortex using previously mapped sensory experiences, as well as integration of cross-modality sensory information. Studies investigating somatosensory feedback during unexpected perturbation during a motor task localized somatosensory error maps to bilateral SMG (Guenther, 2006; Tourville & Guenther, 2011). Further analysis revealed functional connectivity between SMG, ventral PM cortex, IFG and motor cortex (Golfinopoulos et al., 2011). Evidence from structural neuroimaging studies indicates that reduced white matter integrity surrounding SMG bilaterally is associated with stuttering (Cykowski, Fox, Ingham, Ingham, & Robin, 2010; Watkins et al., 2001). In addition, reduced functional neural activation has been reported in the left SMG during both speech and non-speech tasks in individuals who stutter (Braun et al., 1997; Chang et al., 2009; Loucks et al., 2011). Since SMG is a key region involved in sensorimotor integration, its functional connectivity to the motor areas makes it a region of interest in the speech sensorimotor network.

2.4.1.6 Inferior frontal gyrus

IFG consists of three prominent gyri: pars opercularis, pars triangularis, and pars orbitalis. IFG, situated anterior to the lip, tongue, and mouth representations in the motor area, is suggested to be responsible for lexical processing, grammatical processing, and articulatory control required for speech production (Bhatnagar, 2002; Guenther, 2006; Newman & Twieg, 2001). The pars triangularis area is structurally connected with the anterior portion of the HG. Pars opercularis, on the other hand, is structurally connected to the PM areas, superior temporal gyrus, and inferior parietal cortex. It is involved in articulatory control, phonetic coding, syllabification, and assembling of articulation codes (Beal et al., 2010; Glasser & Rilling, 2008; Hickok, 2001; Hickok & Poeppel, 2007). Reduced functional and structural connectivity between IFG and PM regions have been associated with stuttering during overt speaking tasks (Chang et al., 2011; Loucks et al., 2011; Neumann et al., 2005). Temporal reversal of activation of inferior frontal cortex regions and motor cortex was noted in people who stutter even when they were speaking fluently (Salmelin et al., 2000). Therefore, examining the connections between feedforward and feedback regions is crucial to understanding the sensorimotor integration in people who stutter.

2.4.2 Summary of Regions of Interest

From the foregoing evidence, it can be deduced that Heschl's gyrus (HG), Sylvian parietal temporal area (Spt), premotor cortex (PM), inferior frontal gyrus (IFG), supramarginal gyrus (SMG) and rolandic operculum (RO) are functionally connected and form part of a bigger sensorimotor network. HG is considered the primary auditory area, Spt is considered to be the

auditory-motor translator (Hickok et al., 2011; Hickok et al., 2009), PM is activated during motor planning and programming, IFG is involved in articulatory control and phonetic coding, SMG is considered to be somatosensory-motor translator and RO is considered to be involved in somatosensory feedback area. The above-mentioned regions of interest have been reported to be atypically activated in people who stutter. In addition, reduced white matter coherence has been noted surrounding these areas. Connectivity differences between these sensorimotor areas between people who stutter and those who do not have not been examined to date. Examining the connections between sensorimotor regions will help to identify weak links in the network that might lead to stuttering.

2.5 PILOT STUDY

As a first step in assessing weak links in white matter connectivity between these regions, a pilot study was conducted to examine the connections between four sensorimotor regions (HG, Spt, PM and RO) in people who did not stutter. Tract segmentation was performed on eight pre-existing dMRI scans of fluent neurologically healthy adults. Twelve tracts (six in each hemisphere) were mapped between Spt, RO, PM, and HG. Cortical connectivity was measured based on the presence or absence of a connection between regions of interest. Subject-specific analysis of left hemisphere tracts showed consistent cortical connectivity between Spt, PM, RO, and HG, except for Spt-HG, which was only seen in 50% of the participants. Template analysis showed connectivity patterns in accordance with the subject-specific analyses in 4 out of 6 tracts

in the left hemisphere: Spt-RO, RO-PM, Spt-PM, and HG-RO. The template analyses revealed zero tracts for HG-PM and Spt-HG.

Connections in the right hemisphere were consistent with those in the left hemisphere, except for Spt-PM, Spt-HG and HG-PM. Connections for Spt-PM, Spt-HG and HG-PM were seen in 87.5%, 62.5%, and 75.5% of the participants respectively. Template analysis of right hemisphere tracts revealed cortical connectivity between RO-PM and HG-RO only.

The discrepancy between the template and subject-specific analysis could be attributed to the individual variability in cortical folding and connections. The template is an average of 90 participants, so heterogeneity of smaller tracts may not be visible due to averaging. Results from subject specific and template connectivity analysis of tracts for both left and right hemisphere are reported in Table 3.

Table 3: Connectivity Matrix (Pilot Study)

	Spt-RO	Spt-HG	Spt-PM	RO-PM	HG-PM	HG-RO
Left Hemisphere Subject Specific	+++++++	00+0+0++	++++++	+++++++	++++++	++++++
Left Hemisphere Template	+	0	+	+	0	+
Right Hemisphere Subject Specific	+++++++	0++++0+0	++++++0	+++++++	+++++0++	++++++
Right Hemisphere -Template	0	0	0	+	0	+

Note: Spt-Superior parietal temporal region, PM-Premotor region, HG- Heschl's gyrus, and RO-Rolandic operculum. “+” indicates connection and “0” indicates absence of connection

Structural connectivity between RO and Spt allows for the possibility of an interaction between the somatosensory and auditory systems. Similarly, structural connectivity between the feedforward mechanism in the left PM and the feedback mechanisms in Spt and RO, when combined with functional activation studies, points to the synergy between these loops required in planning, programming, and executing speech.

Connections in the right hemisphere were not as consistent as the left hemisphere. These differences in cortical connections could be due to the left hemisphere dominance for speech and language. Although structural connectivity does not necessarily imply functional interaction or integration between sensorimotor regions, the existence of a structural network provides a foundation for examining the interaction between regions involved in speech production. Preliminary analyses indicate that there is a potential network connecting the sensory and motor

areas involved in speech production, namely Spt, RO, PM and HG. These findings provide a foundation for assessing deficiencies associated with stuttering, which is postulated to result from a faulty network. Since these regions are involved in the sensorimotor integration required for speech production, examining the differences in connectivity between these regions will shed light on the deviances seen in people who stutter.

2.6 RESEARCH QUESTIONS

Converging evidence suggests that people who stutter exhibit aberrant activation in HG, posterior superior temporal gyrus, SMG, RO, PM, IFG, primary motor areas and the cerebellum. These areas are involved in planning, initiation, coordination and execution of speech. Converging evidence from structural neuroimaging studies indicate reduced white matter integrity surrounding regions underlying sensorimotor areas involved in speech production. Assessing the white matter connectivity of smaller networks between sensory feedback and motor regions will help to identify the location of disruption in the sensorimotor network. The first step towards achieving this goal is to map the white matter connections between the ROIs: Spt, RO, SMG, PM, IFG and HG.

Research Question #1: Are there structural connectivity differences between people who stutter and people who do not stutter in the white-matter tracts between sensorimotor regions involved in feedforward and feedback pathways, namely IFG, PM, and RO, SMG, Spt and HG?

Hypothesis 1:

Null (H_0): There are no structural connectivity differences between regions involved in the feedforward system in people who stutter compared to people who do not stutter.

Alternate hypothesis (H_1): People who stutter will show connectivity differences between regions in the feedforward system when compared to people who do not stutter.

Hypothesis 2:

Null (H_0): There are no structural connectivity differences between regions involved in the feedback system in people who stutter compared to people who do not stutter.

Alternate hypothesis (H_1): People who stutter will show connectivity differences between regions in the feedback system when compared to people who do not stutter.

Hypothesis 3:

Null (H_0): There are no structural connectivity differences between pathways connecting feedforward and feedback system in people who stutter compared to people who do not stutter.

Alternate hypothesis (H_1): People who stutter will show connectivity differences between pathways connecting feedforward and feedback system in people who stutter compared to people who do not stutter.

Decreased activation patterns and reduced white matter integrity surrounding left hemisphere sensorimotor regions were reported in people who stutter compared to those who do not stutter. In addition, pilot data revealed connections between Spt and PM in 8 out of 8 participants who do not stutter indicating the existence of a structural framework. Experimental evidence also suggests increased and sustained activation in the right sensorimotor areas in people who do stutter. Since function and structure are interdependent, the existence of a structural framework makes functional connections possible.

Converging evidence and sensorimotor models of speech production suggests an interaction not only between the motor and system systems but also between the auditory and somatosensory sensory systems during speech production. It is therefore hypothesized that people who stutter will exhibit reduced connections in both feedforward and feedback loops in the left hemisphere and increased white matter integrity of both feedforward and feedback loops in the right hemisphere.

Research Question #2: Is there a correlation between stuttering severity and adverse impact (as measured by the SSI-4 and OASES-A, respectively) and neural connectivity measure (QA) between sensorimotor regions in people who stutter?

Null (H_0): There will be no correlation between stuttering severity or impact score and neural connectivity differences in people who stutter.

Alternate Hypothesis (H_1): There will be a negative correlation between stuttering severity (SSI-4) and impact score (OASES-A) and neural connectivity measure (QA) in people who stutter.

Because white matter myelination is involved in speed of information transfer between brain regions, and decreased neural activation during speech production is associated with stuttering, it can be hypothesized that there will be a negative correlation between stuttering severity and white matter connections between sensorimotor regions. QA, which represents fiber density and compactness of fiber bundles is used for calculating correlation, as it is a more robust measure than FA (Yeh et al., 2016). OASES-A assesses stuttering severity from the speaker's perspective and SSI-4 measure severity from listener's perspective. The two tools assess different underlying mechanisms: OASES-A measures cognitive processes such as a person's cognitive and affective responses to stuttering while the SSI-4 measures sensorimotor functions.

Due to the variability seen in overt stuttering symptoms, OASES-A was added as an additional measure to capture the impact of stuttering in a person's life.

The proposed study is an important first step in evaluating the neural underpinnings of stuttering using sophisticated technology that will be the springboard for future research. Most structural connectivity studies have focused on prominent fiber tracts postulated to be involved in speech and language such as arcuate fasciculus, middle longitudinal fasciculus or corticospinal pathways (Chang et al., 2011; Fernández-Miranda et al., 2014; Saur et al., 2008; Verstynen, Jarbo, Pathak, & Schneider, 2011). Mapping the smaller sensorimotor networks will enable a fine-grained analysis of the structural integrity of the system and facilitate the identification of regions of potential instability that may result in speech production disorders. For example, reduced white matter integrity surrounding the RO has been noted in disorders such as stuttering (Sommer et al., 2002). As the structural connections of the RO to other regions involved in speech production have not been mapped, it is difficult to assess the integrity of the neural network. Therefore, identifying the neural circuits involved in various stages of speech production is a crucial step towards localizing and assessing extent of inefficiency involved in speech disorders such as stuttering. It also provides a springboard for studying the dynamics between several sensorimotor networks to delineate how the brain compensates for an inefficient system, as may be seen in conditions such as stuttering.

3.0 METHODS

3.1 PARTICIPANTS

Seven people who stutter, mean age 33 years (SD=7.72), two females and five males participated in the study. People who stutter were age- and sex-matched to the people who do not stutter (mean age=33, SD=6.58). Sample size was based on a power analysis that indicated a minimum of 6 participants in each group for a power of 0.8 (Cai et al., 2014). Neuroanatomical scans of the participants was obtained using Diffusion Magnetic Resonance Images (dMRI). The participants were scanned at the Magnetic Resonance Research Center (MRRC) at the University of Pittsburgh. Absence of stuttering history of the control group participants was confirmed by having the participants fill out a self-report questionnaire. Participants were screened for MRI safety and informed consent was obtained.

Table 4: Demographics of participants who stutter

Participants	Age	Sex	Handedness
1	36	M	Right
2	29	M	Right
3	24	F	Right
4	25	F	Right
5	41	M	Right
6	44	M	Right
7	30	M	Right

Table 5: Demographics of participants who do not stutter

Participants	Age	Sex	Handedness
8	38	M	Left
9	34	M	Left
10	117	F	Right
11	30	M	Right
12	28	F	Right
13	25	M	Right
14	45	M	Right

3.2 SPEECH ASSESSMENTS

Stuttering severity and impact of stuttering on speaker's life was assessed using Stuttering Severity Instrument-Fourth edition (SSI-4) (Riley, 2009) and The Overall Assessment of the Speaker's Experience of Stuttering - Adult (OASES-A) (Yaruss & Quesal, 2010). Overt symptoms of stuttering were determined using SSI-4 based on a 300- syllable reading task and a 300- syllable spontaneous speech task. Transcription of the speech samples during both the tasks was obtained based on audiovisual recordings. Speech samples were coded according to SSI-4 instructions. The SSI-4 consists of four sections: frequency of stuttering, duration of stuttering, physical concomitants observed, and naturalness of speech. Frequency was calculated as the average of percent syllables stuttered in three 100- syllable spontaneous speech samples. Duration was derived from the average of three longest stuttering events, timed to the tenth of a second. Types of disfluencies that were coded consisted of syllable or word repetitions, prolongations, and blocks. Four types of physical concomitants were noted: distracting sounds, facial grimaces, head movements, and movements of extremities. Severity was calculated based on scores that are scaled between 2-18 for frequency and duration, and 0-20 for physical concomitants. The total score was calculated by adding the scores for each section and then converted into percentile rank and severity equivalent.

Scores form the SSI-4 ranged from 9-23; two participants scored in the very mild range and five participants scored in the mild range. The Stuttering Severity Instrument may not be a true representation of the stuttering severity as it only accounts for overt stuttering behaviors at a particular point in time. In order to account for this variability the OASES-A was administered to assess the impact of stuttering on one's life.

The OASES-A is a self-report questionnaire consisting of 100 items. The items are scored on a Likert scale from 1-5, with 5 representing a high degree negative impact and 1 represents minimal negative impact of stuttering. It consists of four sections: a) General Information on speaker's overall knowledge and perception of stuttering; b) Reactions to stuttering, which assesses speaker's affective, behavioral and cognitive reactions to stuttering; c) Functional communication difficulty in a variety of situations; and d) impact of stuttering on quality of life. The total number of responses in a section was multiplied by the highest rating on the Likert scale (5) to obtain the maximum possible points that can be obtained in each section. The impact score is a percentage of responses to the total possible points in a section.

Scores on the OASES-A ranged from 1.36-2.98 with 1 participant in the mild range, 1 participant in the mild/moderate range, 5 participants in the moderate range. The OASES assessed the impact of stuttering based on the speaker's perspective. Refer to Table 4 for SSI-4 and OASES-A scores of participants.

Table 6: SSI-4 and OASES-A Scores

Participant	SSI-4	Severity Rating	OASES-A	Overall Impact Rating
1	9	Very Mild	1.95	Mild/Moderate
2	21	Mild	1.36	Mild
3	7	Very Mild	2.76	Moderate
4	13	Mild	2.36	Moderate
5	23	Mild	2.98	Moderate
6	19	Mild	2.65	Moderate
7	20	Mild	2.91	Moderate

All coding and scoring were done by a licensed speech pathologist. A licensed speech language pathologist independently coded and scored 2 (33%) randomly selected speech samples and OASES-A scoring forms to assess inter-rater reliability for the SSI and OASES-A. The inter-rater reliability for SSI-4 scoring was 80.7% and OASES-A was 99% agreement.

Auditory acuity of people who stutter was assessed during a hearing screening. Dichotic digits and words tasks were used to assess dominant ear as people who stutter exhibited hemispheric imbalance when process complex linguistic stimuli. Dichotic Words Test consists of 25 sets of single syllable words. The words were presented dichotically to both left and right ear at 50db HL. The participant was asked to repeat the words in any order and guess the words if they were unsure. The percentage of correct responses was calculated for each ear. The difference between percent correct in the ears was used to assess ear advantage (Moncrieff, Keith, Abramson, & Swann, 2016). Similarly, the Randomized Dichotic Digit test, which consists of 18 sets of numbers, was administered dichotically and ear advantage was calculated.

Hearing screening revealed auditory acuity within normal range for all participants who stutter. Randomized Dichotic Digits Test scores were compared to normative data to determine performance and ear advantage (Strouse & Wilson, 1999). Three participants did not show an ear advantage, three participants exhibited left ear advantage, and one participant exhibited right ear advantage. Four participants scored below normal range in both ears. Results from the Dichotic Words Test were similar to results from the Digits Test, but not all participants who scored below the normal range in the words test scored below normal on the digits test (Table 5). For example, in the Digits Recall Test, participant 2 showed below normal performance in both ears whereas participants 3,5, and 13 showed lower performance scores in the right ear only. In the Words Recall Test, participants 4,5, and 14 showed below normal performances in both ears while participant 2 showed lower performance compared to normative data in right ear only. The percentage of correct responses for Dichotic Words Test and Randomized Dichotic Digits tests are reported in figure 3 and figure 4 respectively.

Atypical processing of auditory information in people who stutter was evidenced by dichotic listening tasks. Four out of seven participants who stutter scored lower than the normal range either in the digits or words task. Two participants showed greater ear asymmetry in digits recall and three participants showed greater ear asymmetry in word recall test. This area should be investigated with a bigger sample size to determine the role of interhemispheric auditory information transfer in stuttering.

Table 7: The Randomized Dichotic Digits Test

Participants	Sex	Age	Left Ear Norms	Left Ear% correct		Right Ear Norms	Right Ear% correct	
1	Male	36	77.5-95.5	100	WNL	92.1-98.1	100	WNL
2	Male	29	94.3-99.5	67	Below Normal	95-100.2	88	Below Normal
3	Female	24	94.3-99.5	94	WNL	95-100.2	88	Below Normal
4	Female	25	94.3-99.5	100	WNL	95-100.2	100	WNL
5	Male	41	81.2-95.4	100	WNL	89.8-98.7	78	Below Normal
6	Male	44	81.2-95.4	94	WNL	89.8-98.7	88	Below Normal
7	Male	30	77.5-95.5	93	WNL	92.1-98.1	93	WNL

Note: Scores based on normative data (Strouse & Wilson, 1999)

Table 8: The Dichotic Words Test

Participants	Sex	Age	Left Ear Norms	Left Ear % correct		Right Ear Norms	Right Ear % correct	
1	Male	36	70-79	92	WNL	82-88	96	WNL
2	Male	29	70-79	100	WNL	82-88	80	Below Normal
3	Female	24	76-83	96	WNL	88-91	100	WNL
4	Female	25	76-83	76	WNL	88-91	88	WNL
5	Male	41	70-79	28	Below Normal	82-88	68	Below Normal
6	Male	44	70-79	100	WNL	82-88	92	WNL
7	Male	30	70-79	68	Below Normal	82-88	84	WNL

Note: Based on Normative data of 12 year olds (Moncrieff et al., 2016)

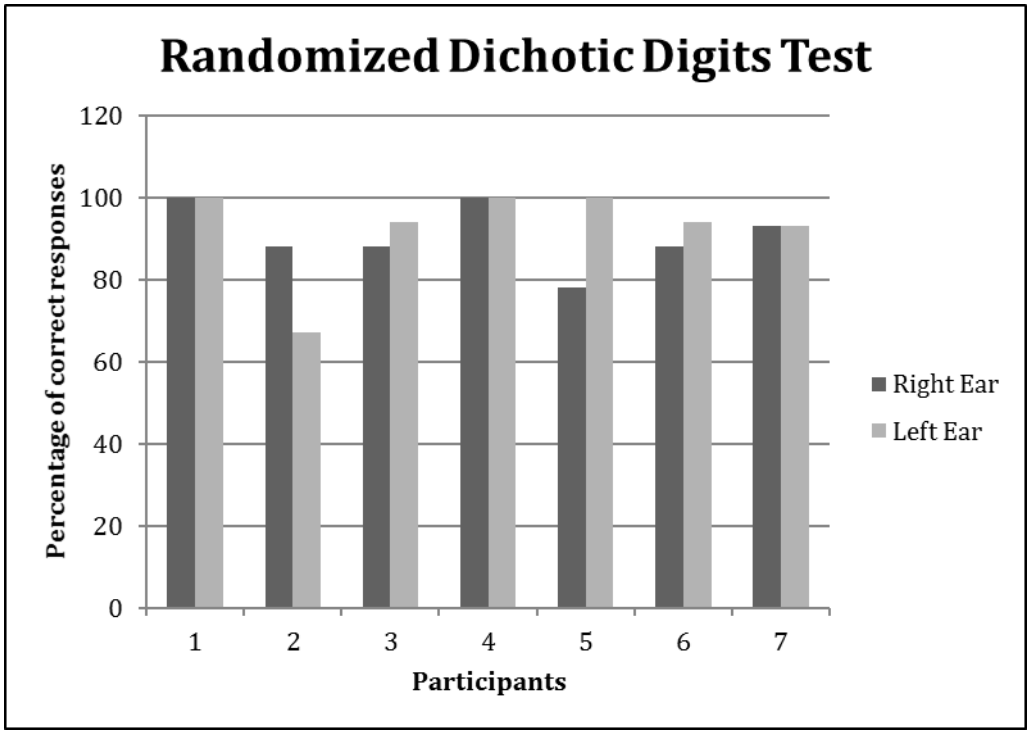


Figure 3: Percentage of correct responses of participants who stutter on Randomized Dichotic Digits Test

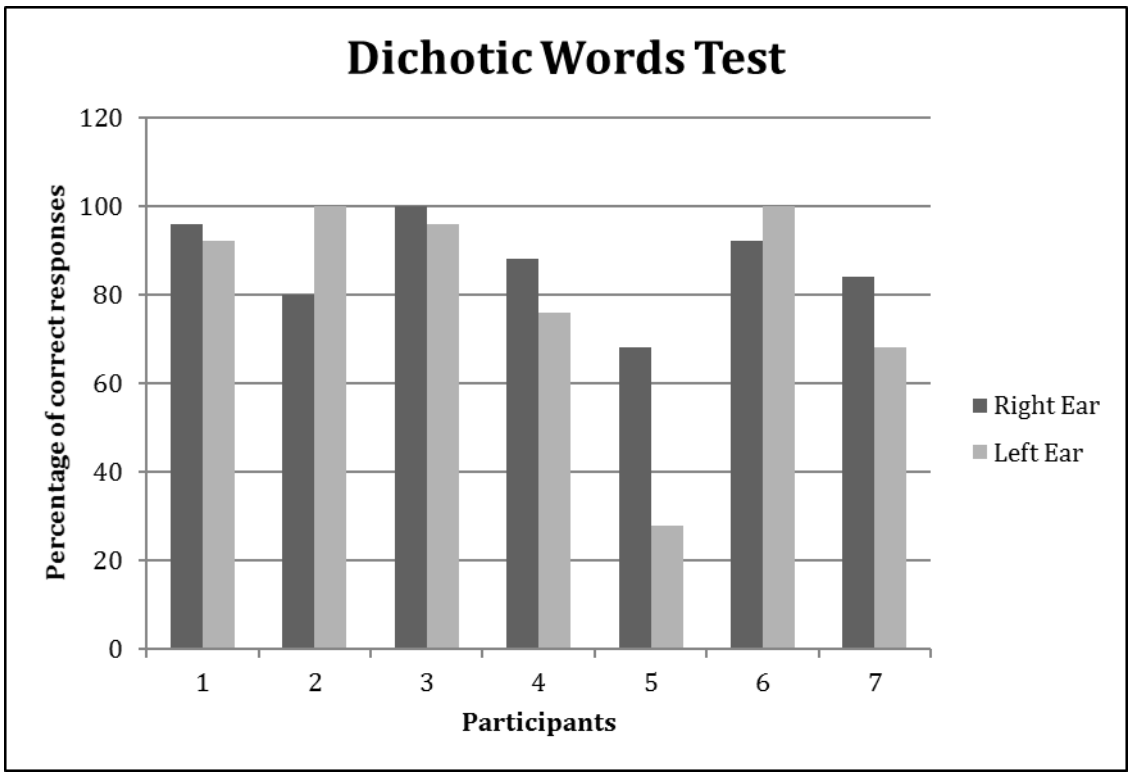


Figure 4: Percentage of correct responses of participants who stutter on the Dichotic Words Test

3.3 STRUCTURAL IMAGING

Structural connectivity between the sensorimotor regions was examined using diffusion Magnetic Resonance Imaging (dMRI). dMRI is a non-invasive imaging technique that measures the diffusion of water in the cerebral white matter tissues (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). As diffusion of water is affected by the microstructure of the tissue, it can reveal the directional orientation of water disbursement in that tissue (Hagmann et al., 2006). Water molecules in the intra- and extra-cellular space contain both isotropic and anisotropic

content. Diffusion in the intra-cellular space can be described using the Probability Distribution Function (PDF) of water displacement (Hagmann et al., 2007). PDF is a six-dimensional quantity, which is radially projected onto a sphere called the Orientation Distribution Function (ODF). The directional component of the anisotropic water is estimated by subtracting the isotropic portion of water from the total water content represented in a voxel. The anisotropic quality of water forms several orientation peaks along different axes. The strength and direction of these peaks are measured using quantitative anisotropy (QA) (Yeh, Wedeen, & Tseng, 2010), which resolves limitations such as inaccuracies in assessing multiple fiber crossing (Abhinav et al., 2014).

3.3.1 Image Acquisition and Reconstruction

Diffusion Spectrum Imaging data was acquired on 3T Tim trio system (Siemens) using a 32-channel coil. The participants were scanned for 30 minutes. The scanning procedure involves a 257-direction scan, using a twice-focused spin-echo Echo Planar Imaging (EPI) sequence and multiple *q* values (Repetition Time (TR)=9,916 ms, Echo Time (TE)=157 ms, voxel size=2.4X2.4X2.4 mm, Field of View (FoV)=231X231 mm, b-max=7,000s/mm^2). For anatomical comparisons, high-resolution anatomical imaging was also included, by employing a 9-min T1-weighted axial MPRAGE sequence (TR=2,110 ms, TE=2.63 ms, flip angle=8^0, 176 slices, FoV=256X256 mm^2 voxel size = 0.5 X0.5 X 1.0 mm^2). Generalized Q sampling Imaging (Feng et al., 2011) was used to reconstruct the DSI data (Yeh et al., 2010). The ODFs were reconstructed to 362 discrete sampling directions and a mean diffusion distance ratio of 1.2 (Verstynen et al., 2011). Both GQI and ODF reconstruction was done using DSI studio (http://dsi

studio.labsolver.org) (Yeh, Verstynen, Wang, Fernández-Miranda, & Tseng, 2013; Yeh et al., 2010).

3.3.2 Fiber Tracking and Segmentation

The cortical connectivity of 15 tracts will be segmented for both hemispheres. Interhemispheric connectivity between corresponding regions were also segmented. Thus, this study involves fiber tracking and segmentation for 36 tracts in total (Table 6).

Fiber tracking and tract segmentation was completed manually using DSI Studio (http://dsi studio.labsolver.org) (Yeh et al., 2013; Yeh et al., 2010). Tract parameters were set to generate tracts with minimum false fibers and facilitate accurate quantification of the segmented tracts. False fibers include fibers that terminate prematurely, fibers that do not follow the turning parameter, and fibers that do not terminate in the end ROI. The technical parameters that was adjusted in this investigation included: ROI seed region, ROI end region, step size, number of seeds, QA threshold, maximum angle, tract length, and smoothing. Tract parameters such as number of seeds, step size, smoothing, and length of fiber were constant across participants and tracts, except for QA threshold, which varied by subject, and maximum angle, which varied by tracts. QA, a stopping criterion, was set by subject in order to account for variations in scanner sensitivities and diffusion signals. Maximum angle, the angle at which all turning fibers will be included, was set by tract to make the comparison consistent across participants. Tracking parameters are discussed in detail below.

Table 9: Tracts that will be segmented in one hemisphere

	Spt	SMG	RO	HG	PM	IFG
Spt	RSPT-LSPT	Spt-SMG	Spt-RO	Spt-HG	Spt-PM	Spt-IFG
SMG		RSMG-LSMG	SMG-RO	SMG-HG	SMG-PM	SMG-IFG
RO			RRO-LRO	RO-HG	RO-PM	RO-IFG
HG				RHG-LHG	HG-PM	HG-IFG
PM					RPM-LPM	PM-IFG
IFG						RIFG-LIFG

3.3.3 ROI Identification

Preloaded ROIs were identified using Automated Anatomical Labeling (http://www.cyceron.fr/index.php/en/plateforme-en/freeware). in DSI Studio. Left Spt was manually drawn according to MNI coordinates (-51, -42, 21) specified in Buchsbaum et al, 2011. The right Spt, which is more lateral and posterior to the superior temporal gyrus than left Spt, was also manually drawn using MNI coordinates (58, -30, 22). The MNI coordinates for the right Spt is based on unpublished preliminary data observed by Buchsbaum et al. Figure 5 shows the ROIs on the left hemisphere: green represents PM, blue represents RO, yellow represents HG, and pink represents SMG. The direction of the fiber propagation between ROIs was randomly set DSI studio, as the purpose of this project was to show the structural connectivity between Spt, HG, RO, SMG, PO and PM, with no specific directionality.

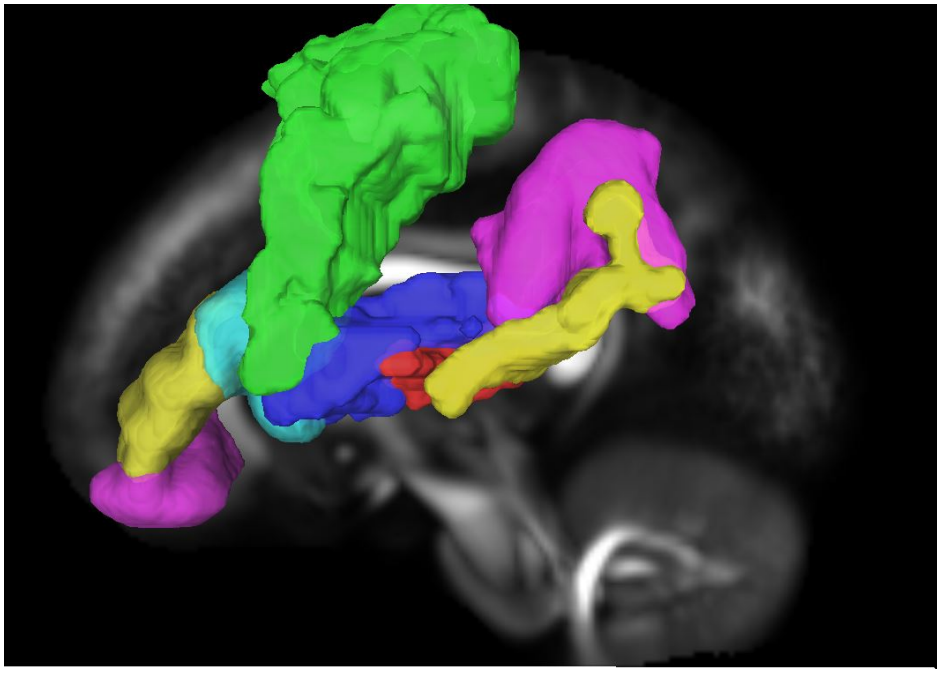


Figure 5: Rendering of regions of interest using Automated Anatomical Labeling in DSI studio

Note: Left hemisphere regions of interest: Green – Premotor (PM), Blue – Rolandic operculum (RO), Pink – Supramarginal gyrus (SMG), Red – Sylvian parietal temporal region (Spt), combination of pink, yellow and blue- IFG and Yellow – Heschl's gyrus (HG) (http://www.cyceron.fr/index.php/en/plateforme-en/freeware).

3.3.4 Seeding

In order to increase the number of the fibers generated, a local seeding approach was used to localize connections between ROIs, rather than a whole-brain seeding approach. Local seeding samples the originating ROI to initiate tracking, whereas whole-brain seeding samples the entire brain. For instance, with global seeding, 700,000 seeds will be spread over the entire brain. With

local seeding, 700,000 seeds will be concentrated within the originating ROI. Since the ROI covers a smaller area than the entire brain, the number of fibers generated will be denser. The process of fiber tracking was started by randomly seeding the voxels covering the origination ROI. *Number of seeds* was one of the tract parameters that was used to determine when the fiber tracking should stop. Using seeds instead of tracts ensured that all possible tracts were generated from the origination area. For example, if 10,000 tracts were selected as the tract parameter, the computer program would stop generating fibers after it generated 10,000 fibers, resulting in inaccurate quantification of the tract if the fiber bundle contains more than 10,000 fibers. The value of 700,000 seeds was obtained by applying various levels of the *number of seeds* parameter (400,000, 500,000, 600,000, 700,000, 1,000,000) to obtain the best visual resolution of the tracts (Greenberg et al., 2012).

3.3.5 Step size

Step size, or rate of fiber progression, was set at 1.2mm, which is one-half of one voxel (Abhinav et al., 2014; Verstynen et al., 2011; Wang et al., 2013). A step size of 1.2 mm is considered optimal, as a value greater than 1.2mm would result in skipping of voxels during fiber tracking, and a step size smaller than 1.2mm would result in inefficient use of resources without significant changes in tract resolution (Wedeen et al., 2008).

3.3.6 Length of tracts

Minimum tract length was set at 20mm to eliminate false fibers, which includes fibers that end within a voxel (Fernandez-Miranda et al., 2010; Verstynen et al., 2011). Since average white matter path length is considered to be 108 mm (Standard Deviation =27 mm), the maximum tract length was set at 300mm to ensure full coverage of tracts (Pannek et al., 2011).

3.3.7 Smoothing

Smoothing in the context of HDFT refers to the momentum of fiber progression. The use of smoothing enables the generation of a tract without sharp turns and angles. For instance, when a smoothing of 0% is applied, the direction of fiber progression is independent of the incoming fiber's direction; in contrast, for a smoothing value of 100%, the direction of fiber progression is fully based on the incoming fiber orientation. For this study, smoothing was set at 20% of the previous incoming fiber and 80% of the nearest fiber's orientation. A pilot study by (Greenberg et al., 2012) suggested that 80/20% is a reliable setting to obtain good coverage of anatomically possible fibers.

3.3.8 Maximum angle

If the current progression of a bundle of fibers has multiple orientations, the angle at which all the turning fibers would be included is called the maximum turning angle. The maximum turning

angle of fiber orientation was constant across participants to make comparison across participants meaningful (Verstynen et al., 2011). Optimal maximum angle parameter per tract was determined during pilot study by using various levels of maximum angle (40°, 55°, 60°, 65°, 70°, 75°, 80°, 85°, 90°, 95°) to generate the maximum total number of fibers with the least number of false fibers.

3.3.9 QA threshold

The fiber tract progression was repeated until the quantitative anisotropy (QA) of the fiber orientation drops below a preset threshold (Yeh et al., 2010). Quantitative anisotropy (QA) value is an indirect measure of the anisotropy diffusion of water in a resolved fiber. It is also a sensitive stopping criterion, as the directional anisotropy value is not averaged at the voxel level, as in the case of Fractional Anisotropy. In an area such as grey matter that has low anisotropy, there might not be clear tract orientation within a voxel, due to isotropic diffusion of water in the tissue (Mori & van Zijl, 2002). As a result, the orientation of the strongest principal axis becomes susceptible to noise when it terminates in grey matter. Therefore a QA threshold higher than the gray matter QA was used as a stopping criterion. QA threshold was selected per subject depending on the relative signal-to-noise ratio in each scan, in order to account for variations in scanner sensitivities and diffusion signals (QA range: 0.52 to 0.32) and ensure full white matter coverage (Abhinav et al., 2014). QA thresholds for the participants are reported in Table 7.

Table 10: QA thresholds by participant

Participants	QA threshold
1	0.029
2	0.03
3	0.04
4	0.037
5	0.02
6	0.032
7	0.033
8	0.033
9	0.035
10	0.05
11	0.03
12	0.036
13	0.023
14	0.02118

3.3.10 Trimming Criteria

Since trimming parameters have not been documented in the literature, stringent trimming criteria was used in this study. Only fibers that start in the seed ROI and terminate at the end ROI will be included. Fibers that do not end in the end ROI were deleted. Fibers that loop around as a result of leniency in setting the maximum angle or QA threshold parameters were trimmed, as these are judged to be false continuations and false fibers. Figures 6 and 7 show raw and trimmed tracts between PM and Spt.

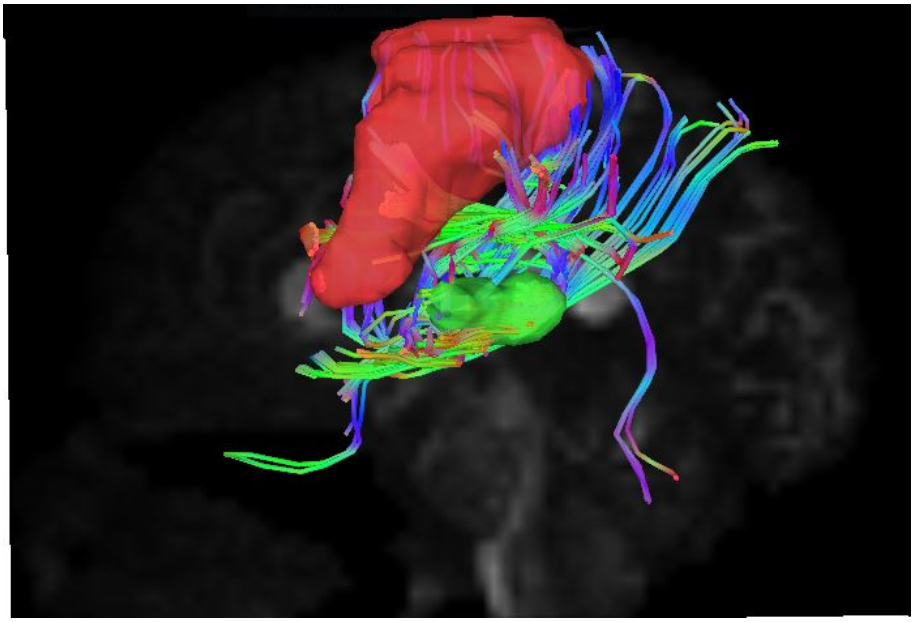


Figure 6: Rendering of untrimmed tracts (DSI Studio)

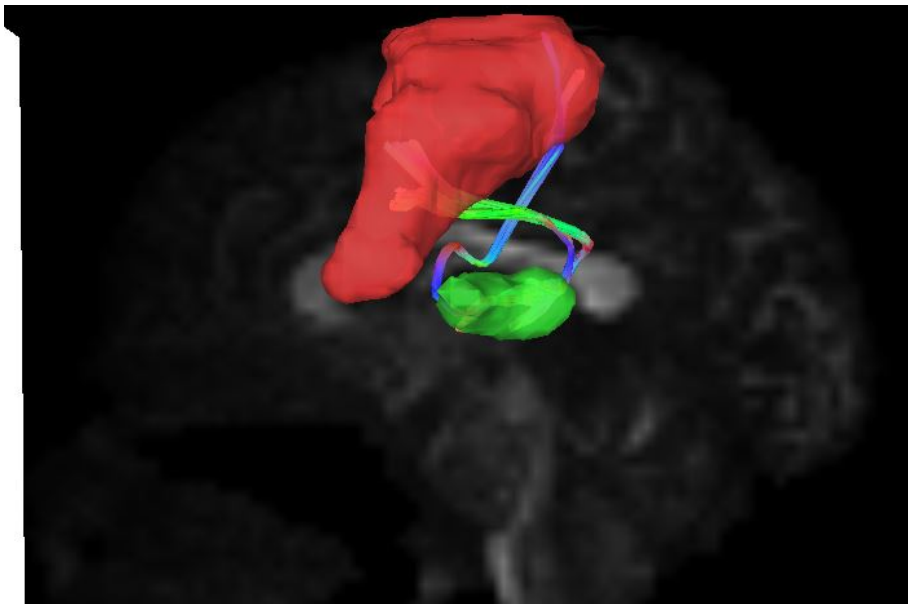


Figure 7: Rendering of trimmed tracts (DSI Studio)

3.3.11 Summary of fiber tracking and segmenting

Fiber tracking was started using DSI Studio by randomly seeding the region of interest with 700,000 seeds. Progression of the fiber was set at a step size of 1.2 mm, minimum length of 20 mm, maximum length of 200 mm, and tract smoothing of 20% of previous moving direction and 80% of incoming direction. Maximum turning angle was set by tract to minimize generation of false fibers. QA termination threshold was set by participant to account for scanner sensitivities and obtain maximum white matter coverage. Once the fibers were generated, the tracts were trimmed based on trimming criteria. All raw and trimmed tracts were saved. A summary of the tracking parameters is reported in Table 8.

Table 11: Summary of tract parameters

Tracts	Number of seeds	Maximum angle	Smoothing	Length of tracts	Seed region	End region
Spt-SMG	700,000	60^0	20	20-300mm	Spt	SMG
Spt –RO	700,000	75^0	20	20-300mm	Spt	RO
Spt-HG	700,000	65^0	20	20-300mm	Spt	HG
Spt -PM	700,000	85^0	20	20-300mm	Spt	PM
Spt-IFG	700,000	60^0	20	20-300mm	IFG	Spt
SMG-RO	700,000	60^0	20	20-300mm	SMG	RO
SMG-HG	700,000	60^0	20	20-300mm	SMG	HG
SMG-PM	700,000	65^0	20	20-300mm	SMG	PM
SMG-IFG	700,000	70^0	20	20-300mm	IFG	SMG
HG-RO	700,000	65^0	20	20-300mm	HG	RO
RO-PM	700,000	90^0	20	20-300mm	RO	PM
RO-IFG	700,000	55^0	20	20-300mm	IFG	RO
HG-PM	700,000	85^0	20	20-300mm	HG	PM
HG-IFG	700,000	70^0	20	20-300mm	IFG	HG
PM-IFG	700,000	80^0	20	20-300mm	IFG	PM

Note: Track parameters. Spt: Sylvian parietal temporal region, SMG: supramarginal gyrus, RO: rolandic operculum, PM: premotor cortex, IFG: inferior frontal gyrus, HG: Heschl's gyrus.

Intra-rater reliability was assessed by segmenting 20% of the tracts for two randomly selected scans. A trained research assistant segmented 20% of the tracts of two randomly selected scans to assess inter-rater reliability. Two-tailed paired sample t tests were conducted to assess inter-rater reliability for a total of 12 tracts in 2 participants. There was no significant difference in the QA, FA or tract volume between the raters for the chosen tracts. Please see table 9 for t statistics and p values for inter-rater reliability testing ($p>.05$).

Table 12: Reliability testing between 2 raters for 2 participants

	PARTICIPANT 1		**PARTICIPANT 2**	
	t statistic	p value	t statistic	p value
Volume	1.49	0.21	1.66	0.17
QA	1.38	0.24	0.22	0.83
FA	1.48	0.21	0.21	0.84

3.4 DATA ANALYSES

The cortical tracts were saved in DSI studio (http://dsi-studio.labsolver.org). Several measures were used to quantify the tracts and end point connectivity: axonal volume, Fractional Anisotropy (FA), and Quantitative Anisotropy (QA). Since intra-cellular water content is directly correlated to axonal volume, mean axonal volume will be used to measure the degree of connectivity between regions. Therefore, a reduction in tract volume is representative of neuro-degeneration. Mean FA, which is calculated by averaging the standard deviation of the anisotropy in a voxel, is a scalar value provides a measure of the directionality of the fiber within a voxel. A value close to zero represents isotropic diffusion (e.g., Corpus Callosum), and a value closer to one means that diffusion occurs along one axis and is fully restricted in all the other directions (e.g., Arcuate fasiculus). Evidence indicates that FA closely represents fiber density, axonal diameter and white matter myelination (Beaulieu, 2002). Hence, mean FA was used to quantify the degree of anisotropy in a fiber tract. Therefore, a reduction in FA represents a change in the tissue such as de-myelination. Mean QA, which is a measure of anisotropy diffusion of water in the cerebral tissues is another indirect quantitative measure of white matter

integrity. Unlike FA, which provides voxel-wise measurement of water diffusion in a voxel, QA provides water diffusion information along the entire fiber. It is based on the spin density, which relates to the number of precessing hydrogen nuclei that contribute to the MR signal. As a result it is a measure of how much water diffuses along a fiber and is representative of density of white matter fibers (Yeh et al., 2016). It provides robust contrast between grey and white matter thereby reducing false continuations of fiber tracts and providing more accurate end point projections when compared to FA.

The absence or presence of a connection was assessed based on modified exclusive “or” (mXOR) (Cieslak et al., 2015). Only the tracts that pass through the registered ROI were included in determining if a connection exists or not. m(XOR) was then used to calculate presence or absence of connection The XOR (exclusive OR) has two binary variables (i.e., people who stutter vs people who do not stutter and presence or absence of streamlines). The modified XOR allows for one deviation from the group pattern. For example, in table 8, if nine out of ten participants in the control group show a connection and ten out of ten participants in the stuttering group do not show a connection between region of interests then the analysis results in an absence of connection (Cieslak et al., 2015).

Table 13: m(XOR) connectivity table

	Presence or absence of fibers									
Control	+	+	+	+	+	+	+	+	+	-
Stuttering	-	-	-	-	-	-	-	-	-	-

Note: Example of a tract that would be considered absent in participants who stutter

3.5 STATISTICAL ANALYSES

Research question #1, which investigated connectivity differences between people who stutter and those who do not, was assessed using non-parametric Mann-Whitney U (Axonal volume QA, FA) with significance level of 0.05. Mann-Whitney U was used due to the cortical anatomy variations reported across fluent as well as individuals who stutter (Catani & de Schotten, 2012). This heterogeneity in the cortical anatomy violates the assumptions of normality, homogeneity of variance, and outliers. Effect size (Cohen's r) was also calculated for each comparison to quantify the extent of difference between the two groups.

Research question #2, which will investigate the correlation between stuttering severity and impact (SSI-4 and OASES-A) and neural connectivity measure (QA) in people who stutter, will be calculated using Spearman's Rho. Correlations will be performed for all 30 tracts, 15 in each hemisphere. Since the heterogeneity of cortical folding violates the assumption of normality

Spearman's Rho was used instead of Pearson Product correlation, which is more susceptible to violations of the assumptions.

The Bonferroni correction, which is used to control type 1 error, involves dividing the family-wise error rate (alpha=0.05) by the number of tests (15 per hemisphere- one for each tract compared). However, due to the small sample size of this study, a Bonferroni correction is extremely restrictive, therefore the correction was not calculated. The results of this study are considered preliminary and provide a foundation for replication in a larger sample**.**

4.0 RESULTS

4.1 STRUCTURAL IMAGING

White matter connectivity measures FA, QA, and tract volume were calculated based on tractography data. Tract segmentation was performed between 6 regions: PM, Spt, IFG, RO, HG and SMG. A total of 36 tracts were segmented: 15 tracts in each hemisphere and 6 inter-hemisphere tracts (Table 6, section 3.3.2).

4.1.1 Fractional Anisotropy (FA)

Comparisons of the tracts in the left hemisphere yielded significant differences between people who stutter and those who do not ($U= 7$, $p= .03$, $r= -0.598$). Specifically, people who stutter exhibited lower FA in the white matter connecting RO to PM. No significant differences ($p > .05$) were found between the two groups in the right hemisphere.

4.1.2 Quantitative Anisotropy (QA)

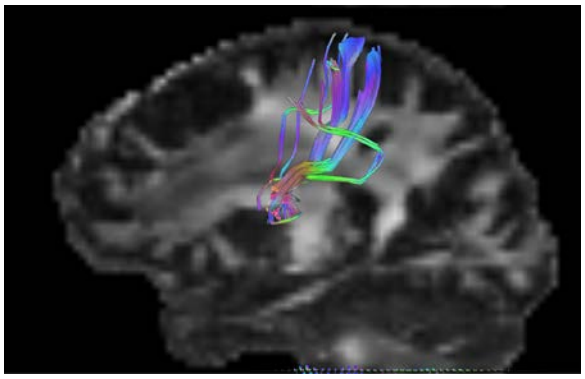
No significant between-group differences ($p > .05$) were seen in QA of the white matter tracts in either of the hemispheres.

4.1.3 Tract volume

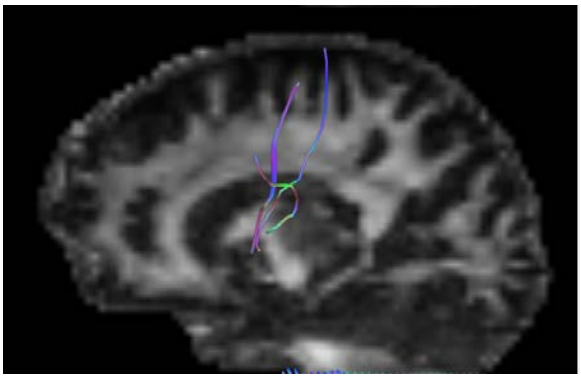
Significant between-group differences were found in volume of tracts bilaterally. In the left hemisphere, a decrease in volume of white matter tracts connecting Spt to RO (U= 9, p= 0.05, r= -0.53) and Spt to SMG (U= 5, p= 0.01, r= -0.67) was seen in people who stutter when compared to people who do not stutter. Similarly, comparisons of tract volume in the right hemisphere showed a decrease in the volume of tracts connecting Spt to HG in people who stutter than for people who do not stutter (U= 8, p= 0.03, r= -0.57). Z-scores and p-values from Mann-Whitney U tests, and Cohen's r for each tract segmented are reported by hemisphere in Tables 11, and 12. Differences in tract volume and FA are shown in Figures 8 and 9.

Participant who does not stutter

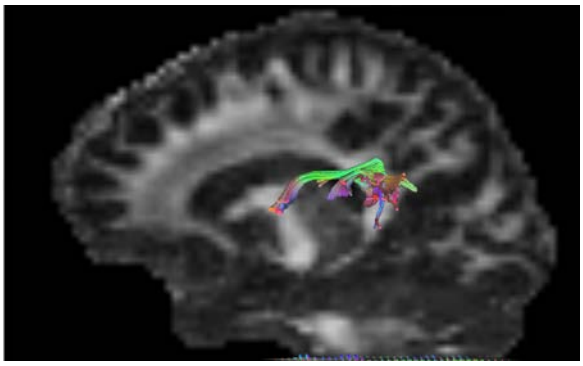
Participant who stutters



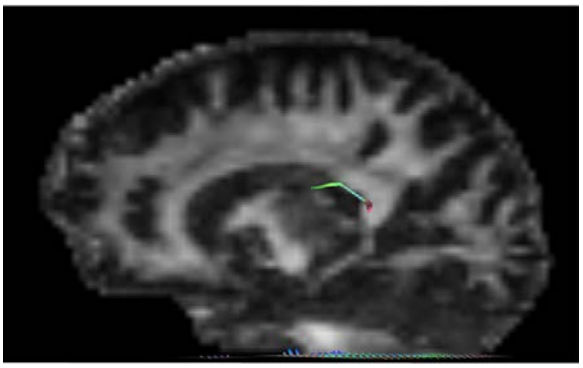
Left RO-PM



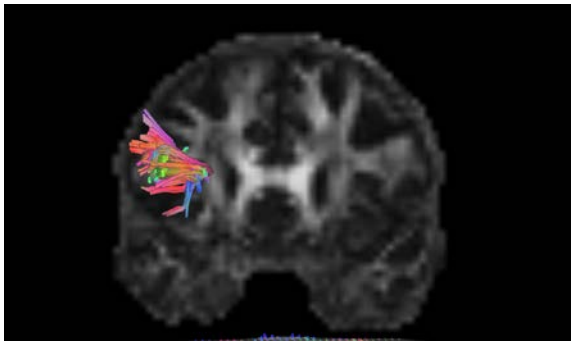
Left RO-PM



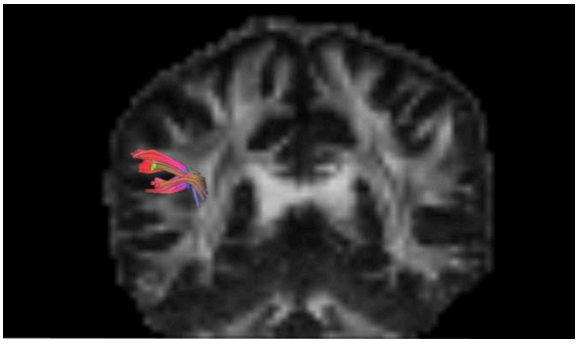
Left Spt-RO



Left Spt-RO



Left Spt-SMG



Left Spt-SMG

Figure 8: Comparison of left hemisphere tracts segmented using HDFT

Note: A significant difference between a participant who stutters (03) and a participant who does not stutter (12). The participants are age and sex matched (Female; mean age 26). Top row: Sagittal view. Significantly lower FA of Left RO-PM was noted in people who stutter when compared to people who do not stutter (z= -2.24, p= .03). Middle row: Sagittal view. Significantly lower tract volume of left Spt-RO was found in people who stutter compared to people who do not stutter (z= -1983, p= .05). Bottom row: Axial view. Significantly lower tract volume left Spt-SMG was noted in people who stutter compared to people who do not stutter (z= -2.492, p= .02)

Person who does not stutter

Person who stutters

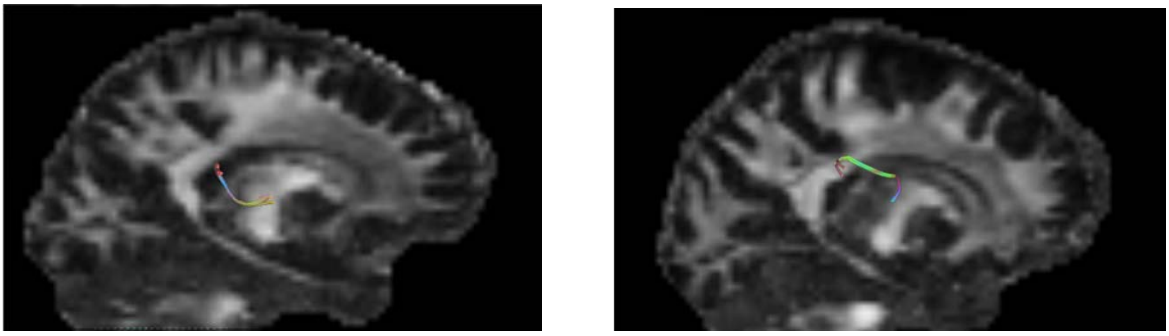


Figure 9: Comparison of right hemisphere tract Spt-HG

Note: Sagittal view of a significant difference in tract volume between a participant who stutters (03) and a participant who does not stutter (12). The participants were age and sex matched (Female; mean age 26). Significantly lower tract volume was noted in people who stutter compared to people who do not stutter (z= -2.13, p= .03).

There were no significant differences in interhemispheric connections between groups (p > .05). Please refer to Table 13 for Mann Whitney U statistics for interhemispheric comparisons.

Table 14: Mann-Whitney U test z and p values of left hemisphere FA, QA and tract volume of tracts "*" denotes p≤ .05 (two-tailed)

Tract	FA			QA			Volume		
Left hemisphere	z value	P value	Effect Size (r)	z value	P value	Effect Size (r)	z value	P value	Effect Size (r)
HG TO PM	-0.06	0.95	-0.02	0.83	-0.41	-0.22	-0.32	0.75	-0.09
HG TO RO	-1.09	0.28	-0.29	-0.70	0.48	-0.19	-0.26	0.80	-0.07
IFG TO HG	1.45	0.14	0.39	1.47	0.14	0.39	1.47	0.14	0.40
IFG TO PM	0.32	0.75	-0.09	-0.58	0.58	-0.16	-1.34	0.18	-0.36
IFG TO RO	-0.32	0.75	-0.09	-0.83	0.41	-0.22	-0.48	0.66	-0.13
IFG TO SMG	-0.84	0.40	-0.22	-0.07	0.95	-0.02	-0.71	0.48	-0.19
IFG TO Spt	-0.13	0.90	-0.03	-0.52	0.61	-0.14	-0.39	0.70	-0.10
RO TO PM	-2.24	0.03*	-0.60	-0.32	0.75	-0.09	-1.09	0.28	-0.29
SMG TO HG	-0.07	0.95	-0.02	-0.85	0.40	-0.23	-0.46	0.65	-0.12
SMG TO RO	-0.06	0.95	-0.02	-0.48	0.66	-0.12	-0.48	0.66	-0.12
Spt TO HG	-0.80	0.42	-0.21	-0.62	0.53	-0.17	-0.44	0.66	-0.12
Spt TO PM	-0.06	0.95	-0.02	-0.58	0.56	-0.15	-0.83	0.40	-0.22
Spt TO RO	-0.58	0.57	-0.15	-0.32	0.75	-0.09	-1.98	0.05*	-0.53
Spt TO SMG	-0.32	0.75	-0.09	0.32	0.75	-0.09	-2.49	0.01*	-0.67
SMG TO PM	-0.98	0.33	-0.26	-1.37	0.17	-0.37	0.59	0.56	0.16

Note: Left hemisphere differences in FA, QA and tract volume of tracts connecting left Inferior frontal gyrus (IFG), Rolandic Operculum (RO), Sylvian parietal temporal (Spt), Heschl's Gyrus (HG), Premotor (PM) and Supramarginal Gyrus (SMG) between people who stutter and those who do not stutter.

Table 15: Mann-Whitney U test z and p values of right hemisphere FA, QA and tract volume of tracts "*" denotes p≤ .05 (two-tailed)

Tract	FA			QA			Volume		
Right Hemisphere	Z value	P value	Effect Size (r)	z value	P value	Effect Size (r)	z value	p value	Effect Size (r)
HG TO PM	-1.04	0.30	-0.28	1.62	0.11	-0.43	-1.86	0.06	-0.50
HG TO RO	-0.19	0.85	-0.05	1.92	0.85	-0.03	-0.83	0.46	-0.22
IFG TO HG	-1.04	0.30	-0.28	1.36	0.17	-0.36	-1.2	.023	0.32
IFG TO PM	-0.32	0.75	-0.06	0.07	0.95	-0.02	-0.19	0.85	-0.05
IFG TO RO	-1.60	0.11	-0.43	0.45	0.66	-0.12	-0.19	0.85	-0.05
IFG TO SMG	-0.96	0.34	-0.26	1.34	0.18	-0.36	-1.47	0.14	-0.39
IFG TO Spt	-0.58	0.57	-0.15	1.47	0.14	-0.39	-0.45	0.65	-0.12
RO TO PM	-0.83	0.41	-0.22	0.19	0.85	-0.05	-0.70	.48	-0.19
SMG TO HG	-0.77	0.44	-0.21	0	1	0	-0.38	0.70	-0.10
SMG TO RO	0.45	0.66	-0.12	0.19	0.85	-0.05	-0.70	0.48	-0.19
Spt TO HG	-1.36	0.18	-0.36	-1.74	0.08	-0.47	-2.13	0.033*	-0.57
Spt TO PM	-0.32	0.74	-0.09	-0.83	0.40	-0.22	-1.35	0.18	-0.36
Spt TO RO	-1.34	0.18	-0.36	-0.83	0.41	-0.22	-1.21	0.23	-0.32
Spt TO SMG	-0.58	0.57	-0.15	-0.45	0.65	-0.12	-0.19	0.85	-0.05
SMG TO PM	-0.83	0.95	-0.22	-0.06	0.65	-0.02	-0.45	0.40	-0.12

Note: Right hemisphere differences in FA, QA and tract volume of tracts connecting left Inferior frontal gyrus (IFG), Rolandic Operculum (RO), Sylvian parietal temporal (Spt), Heschl's Gyrus (HG), Premotor (PM) and Supramarginal Gyrus (SMG) between people who stutter and those who do not stutter.

Table 16: Mann-Whitney U test z and p values of right hemisphere FA, QA and tract volume of tracts "*" denotes p≤ .05 (two-tailed)

Tracts	FA			QA			Volume		
Interhemisphere	z Value	p value	Effect Size (r)	z value	p value	Effect Size (r)	z value	p value	Effect Size (r)
Left HG to Right HG	0	1	0	0	1	0	0	1	0
Left IFG to Right IFG	-1	0.32	-0.27	-1	0.32	-0.27	-1	0.32	-0.27
Left PM to Right PM	0.32	0.74	-0.09	-0.70	0.48	-0.19	-0.58	0.57	-0.15
Left RO to Right RO	-1	0.32	-0.27	-1	0.32	-0.27	-1	0.32	-0.27
Left SMG to Right SMG	-1	0.32	-0.27	-1	0.32	-0.27	-1	0.32	-0.27
Left Spt to Right Spt	0	1	0	0	1	0	0	1	0

Note:
Note: Interhemispheric difference in FA, QA and tract volume of tracts connecting left Inferior frontal gyrus (IFG), Rolandic Operculum (RO), Sylvian parietal temporal (Spt), Heschl's Gyrus (HG), Premotor (PM) and Supramarginal Gyrus (SMG) between people who stutter and those who do not stutter.

4.1.4 Presence or absence of connections

Connectivity was also measured based on whether a connection was present or absent. Presence or absence of the connections were based on m(XOR) (Cieslak et al., 2015). According to m(XOR) there is a difference in connectivity if nine out of ten participants showed a connections and nine out of ten participants who stuttered did not show connection. There were no between-group differences in the connections between the regions of interest in both hemispheres.

Absence of connections was noted between left Spt and HG in six out of seven participants in the experimental group and five out of seven in the control group. Connections were also only observed between left inferior frontal gyrus and Heschl's gyrus in two out of fourteen participants in both groups. In the IFG-HG, six out of seven participants who stutter did not show any connections compared to four out of seven participants in the control group did not show any connections.

4.2 CORRELATIONAL ANALYSES

Significant correlations were found between overall impact scores on the OASES –A and QA of the left Spt-RO (r_S= -0.79, p= 0.04), right IFG-RO (r_S= -0.96, p= 0.00), and right RO-PM (r_S= -0.82, p= 0.02) tracts in people who stutter (Figures 10, 11, and 12). A significant negative relationship was also found between SSI-4 and QA for the left IFG-HG (r_S=-0.80, p= 0.03), IFG-SMG (r_S= -0.76, p= 0.05) and Spt-SMG (r_S= -0.75, p= 0.05) tracts (Figures 13 and 14). Right hemisphere analysis showed negative correlation between SSI-4 and QA for IFG-SPT (r_S= -0.82, p= 0.02) and IFG-PM (r_S= -0.82, p= 0.02) (Figures 15 and 16). Correlation values between QA of tracts and OASES-A, and SSI-4 are reported in Tables 14-17.

Because tract volume differences were noted between people who stutter and those who do not, correlation between stuttering severity and the volumes of the left Spt-RO, left Spt-SMG, and right Spt-HG tracts were analyzed. A significant negative correlation was seen between the volume of left Spt-RO and the total overall score on the SSI-4 ($r_{S=}$ 0.757, p= 0.04). Analyses did not yield any other significant correlation between stuttering severity and the volumes of any of

the other tracts between regions of interest. There were no significant correlations ($p > .05$) between volumes of these tracts and overall impact scores on the OASES-A. Because people who stuttered exhibited significantly lower FA in left RO-PM, post hoc correlations between the FA of the tract and severity, and impact scores were calculated. Correlation analyses between FA of left RO-PM and stuttering severity or impact did not reveal any significant relationships ($p > .05$).

Table 17: Spearman Rho correlational between QA of left hemisphere tracts with OASES-A. '*' denotes $p \leq .05$

	IFG		Spt		HG		RO		SMG		PM	
	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value
IFG			0.19	0.69	-0.09	0.85	-0.43	0.34	-0.56	0.19	-0.68	0.09
Spt					0.41	0.36	-0.79	0.04*	-0.50	0.25	-0.51	0.25
HG							-0.14	0.76	-0.34	0.45	-0.54	0.21
RO									-0.54	0.22	-0.54	0.22
SMG											-0.4	0.38
PM												

Table 18: Spearman Rho correlational between QA of right hemisphere tracts with OASES-A. '*' denotes p≤.05

	IFG		Spt		HG		RO		SMG		PM	
	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value
IFG			-0.29	0.54	0.61	0.14	-0.96	0.00*	-0.68	0.09	0.00	1.00
Spt					-0.43	0.33	-0.25	0.59	-0.07	0.88	0.43	0.33
HG							-0.57	0.18	0.21	0.65	0.13	0.79
RO									-0.14	0.76	-0.82	0.02*
SMG											0.21	0.65
PM												

Table 19: Spearman Rho correlation between QA of left hemisphere tracts with SSI-4 '*' denotes p≤ .05

	IFG		Spt		HG		RO		SMG		PM	
	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value
IFG			-0.41	0.364	-0.80	0.03*	-0.68	0.09	-0.76	0.05*	-0.43	0.34
Spt					0.20	0.66	-0.21	0.65	-0.75	0.05*	0.04	0.94
HG							-0.04	0.94	0.52	0.23	0.14	0.76
RO									-0.61	0.15	-0.47	0.29
SMG											-0.11	0.82
PM												

Table 20: Spearman Rho correlation between QA of right hemisphere tracts with SSI-4
'*' denotes p≤.05

	IFG		Spt		HG		RO		SMG		PM	
	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value	Rho	p value
IFG			-0.82	0.02*	0.61	0.14	-0.39	0.38	-0.43	0.34	-0.82	0.02*
Spt					-0.45	0.31	0.00	1.00	-0.71	0.07	-0.52	0.23
HG							-0.11	0.82	-0.28	0.54	0.02	0.97
RO									-0.61	0.15	-0.57	0.18
SMG											0.21	0.65
PM												

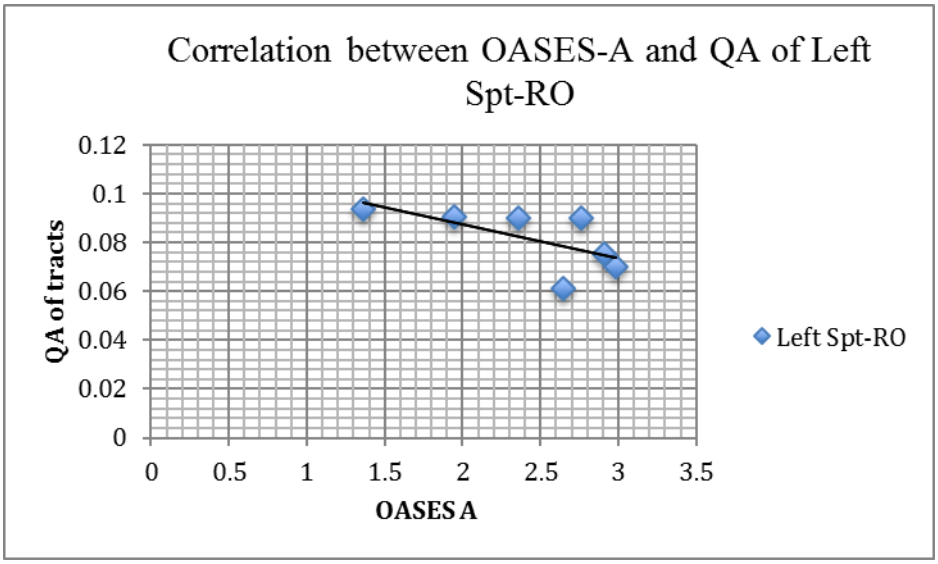


Figure 10: Correlation of overall impact on the OASES-A scores to QA of left Spt-RO in people who stutter (r_S=-0.79, p=0.04)

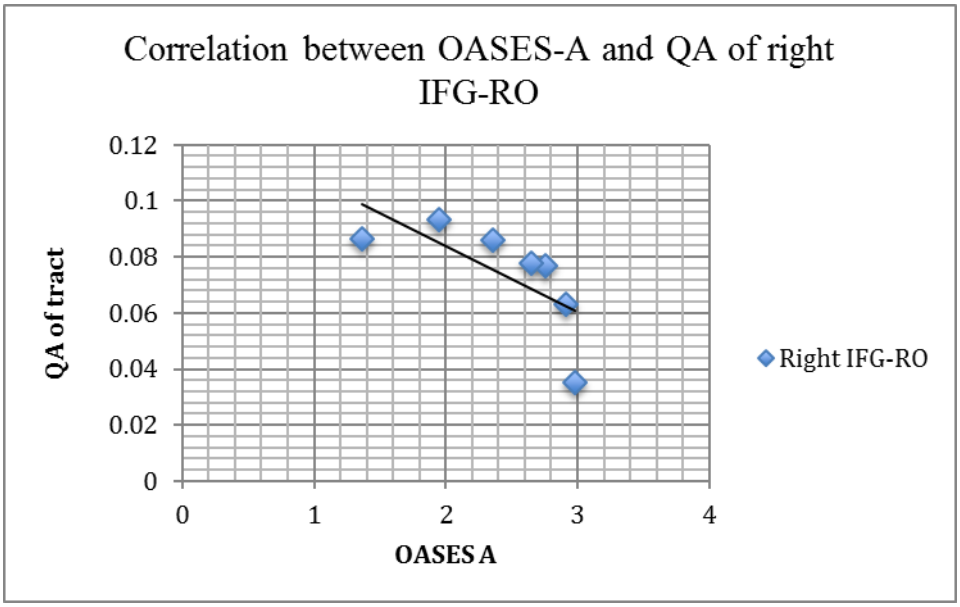


Figure 11: Correlation of overall impact scores on the OASES-A to QA of right IFG-RO in people who stutter (r_S=-0.96, p=0.00)

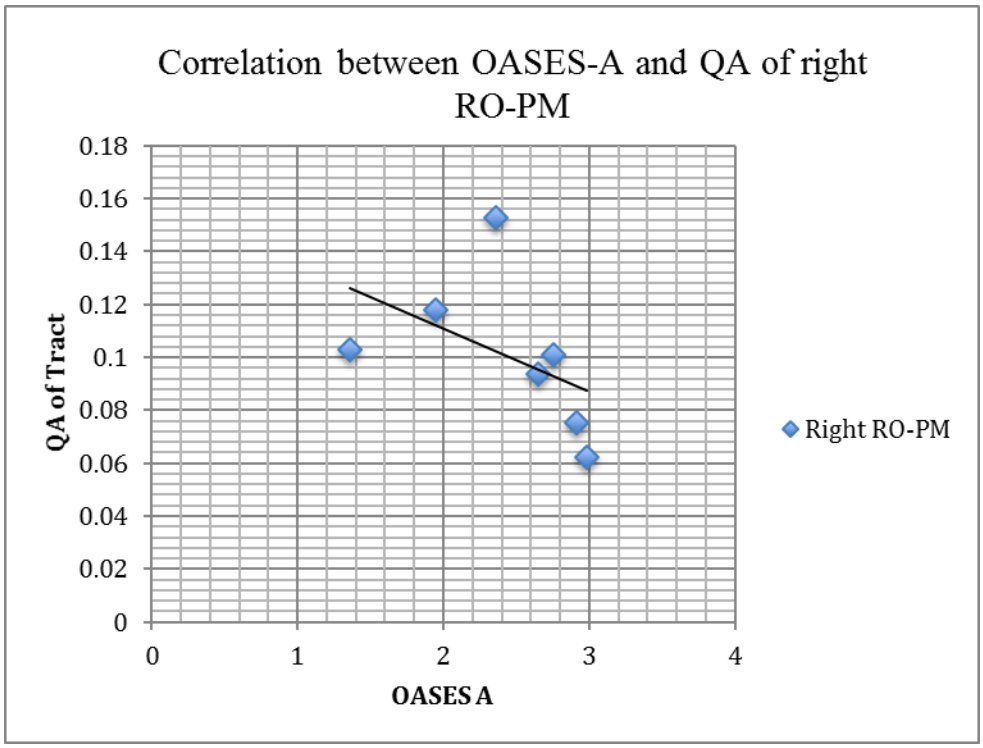


Figure 12: Correlation of overall impact scores on the OASES-A to QA of right RO-PM in people who stutter (r_S=-0.82, p=0.02)

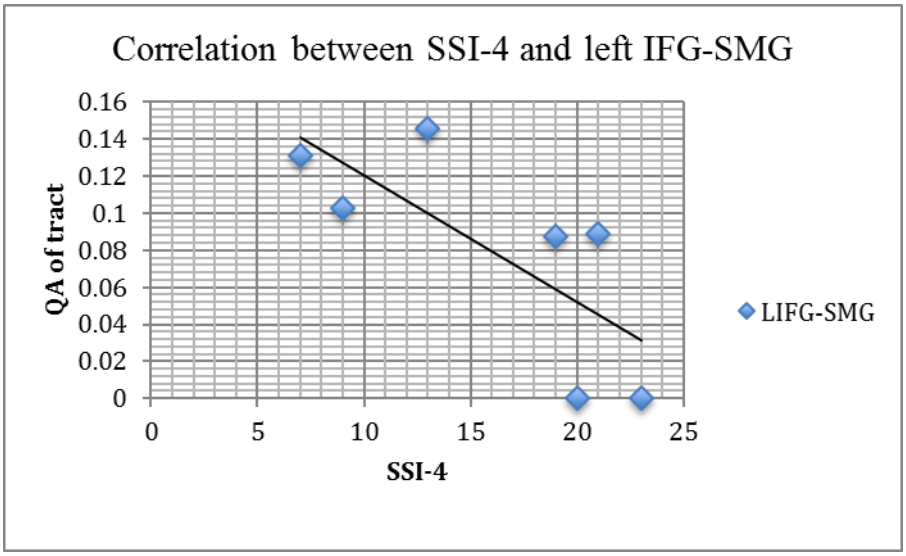


Figure 13: Correlation of scores on SSI-4 to left IFG-SMG in people who stutter (r_S=-0.76, p=0.05)

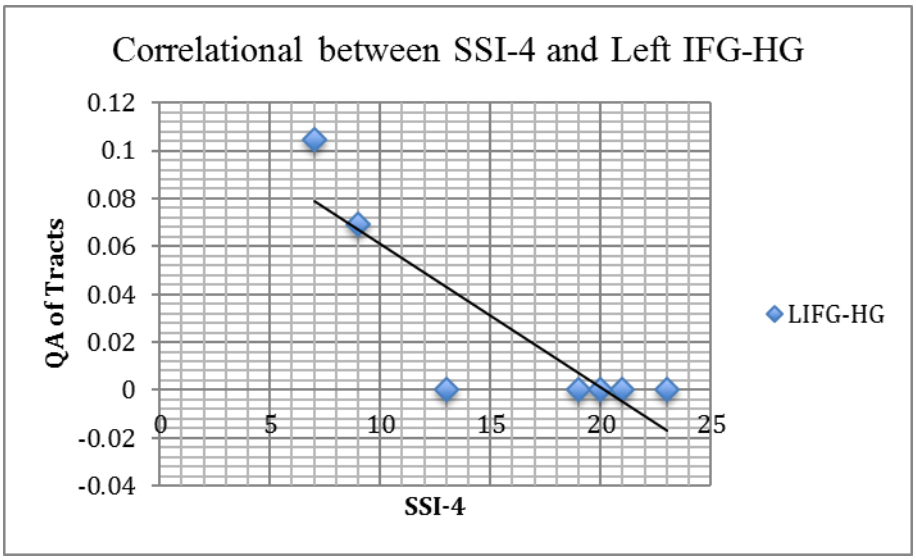


Figure 14: Correlation of scores on SSI-4 to QA of left IFG-HG in people who stutter (r_S=-0.80, p=0.03)

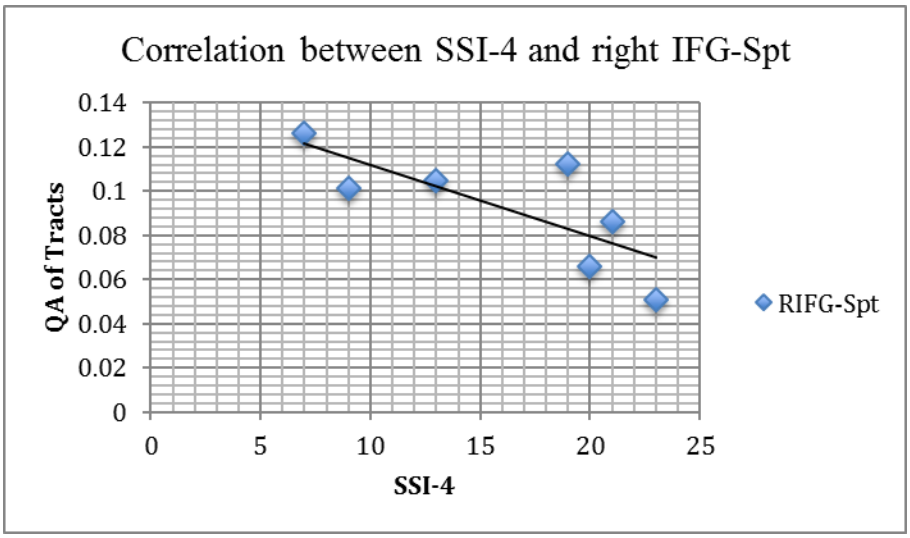


Figure 15: Correlation between SSI-4 and QA of right IFG-Spt in people who stutter. (r_S=-0.82, p=0.02)

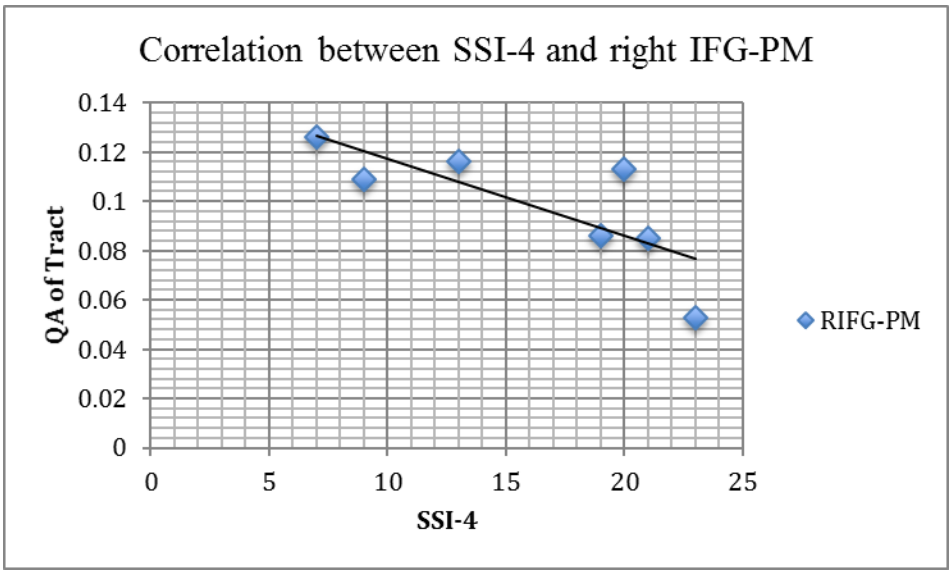


Figure 16: Correlation between QA of right IFG-PM and SSI-4 in people who stutter (r_S=-0.82, p=0.02)

4.3 LATERALIZATION INDEX

Laterality index (LI) of connections of Spt to sensorimotor regions in was performed to assess hemispheric bias in both groups. Lateralization of tract volumes were calculated using

$$LI = \frac{left\ tract\ volume - right\ tract\ volume}{left\ tract\ volume + right\ tract\ volume}$$

Tracts were considered to be left lateralized if LI >0 and right lateralized if LI<0. In order for the bias to be significant a threshold of 0.2 was set. For example, if more than 50% of the group exhibited a left bias of less than 0.2, it was considered a significant left bias. A significant left bias was noted in tract volume of Spt-PM (LI=.07) and significant right bias in Spt-SMG (LI=-.16) in participants who stutter. Participants who do not stutter showed a

significant right bias in tract volume of Spt-RO (LI=-.07), and Spt-SMG (LI=-.06) in participants who do not stutter. Participants who do not stutter also exhibited a significant left bias in tract volume of IFG-Spt (LI=.01). Please refer to Table 19 for Laterality Index of tract volumes.

Table 21: Laterality Index of tract volume in participants who stutter and those who do not stutter

Tract Volume	Participants who stutter	Participants who do not stutter
Spt -PM	0.07	-0.38
Spt-RO	-0.41	-0.07
Spt-HG	-0.67	-0.88
IFG-Spt	0.32	0.01
Spt-SMG	-0.16	-0.06

5.0 DISCUSSION

The heterogeneity in atypical neural activation and behavior manifestation of stuttering have led researchers to postulate that stuttering is the result of a compromised neural network (Biermann-Ruben et al., 2005; Brown et al., 2005; Chang et al., 2009; Foundas, Bollich, et al., 2004; Fox et al., 2000). Since speech is a sensorimotor act, differences in tract volume and white matter FA of pathways connecting sensorimotor regions involved in speech production can lead to atypical processing of information required for rapid, precise, and fluent speech production (Magistro et al., 2015) These atypical activations are posited to result in speech disruptions, such as those seen in stuttering. In order to assess the sensorimotor network associated with stuttering, this study examined the white matter connectivity differences between people who stutter and those who do not stutter in six sensorimotor regions involved in speech production: Spt, HG, PM, RO, SMG and IFG.

5.1 WHITE MATTER INTEGRITY DIFFERENCES BETWEEN PEOPLE WHO STUTTER AND PEOPLE WHO DO NOT STUTTER

5.1.1 White matter volume

5.1.1.1 Left hemisphere comparisons

Results of the study support the hypothesis that people who stutter will exhibit lower white matter integrity of fibers connecting sensorimotor regions in the left hemisphere. In particular, stuttering was associated with reduced volume of fibers connecting left Spt to left somatosensory processing area, SMG (Figure 17). Spt and SMG form part of the auditory and somatosensory feedback system (Guenther, 2006; Tourville & Guenther, 2011). Both regions are associated with processing sensory information based on previously mapped sensory experiences, as well as integration of cross-modality sensory information (Hickok, 2012; Tourville & Guenther, 2011). Both Spt and SMG are posited to be the neural correlates of auditory and somatosensory target and error maps, respectively (Tourville et al., 2008). Bilateral activations of these regions were noted during an overt speaking task with delayed auditory feedback in people who do not stutter (Hashimoto & Sakai, 2003). In addition, sensorimotor models of speech production have proposed interaction between the sensory modalities. Both the DIVA and HSFC models suggest that speech sounds have both auditory and somatosensory target goals. The matching of the expected goals to the current state is done at two levels: the higher auditory feedback at the linguistic level and the lower somatosensory feedback at the motor level. This assertion has been substantiated by behavioral studies that examined the interaction between the two sensory

modalities. In a study investigating the auditory and somatosensory acuity for sibilant production, Ghosh et al. (2010) found that both modalities are important for sibilant production. A negative correlation between auditory feedback and somatosensory feedback was also noted in a study investigating the correlation between auditory and somatosensory feedback during speech production. Furthermore, decreased bilateral SMG activity has been noted in people who stutter compared to people who do not stutter during overt reading tasks (Loucks et al., 2011; Watkins et al., 2008). The functional activation evidence, combined with the decrease in white matter volume of tracts connecting the Spt and SMG noted in this study, could be indicative of a weak interaction between the two sensory systems in people who stutter. The weak interaction resulting from reduced tract volume may result in an inefficient gating mechanism between sensory modalities.

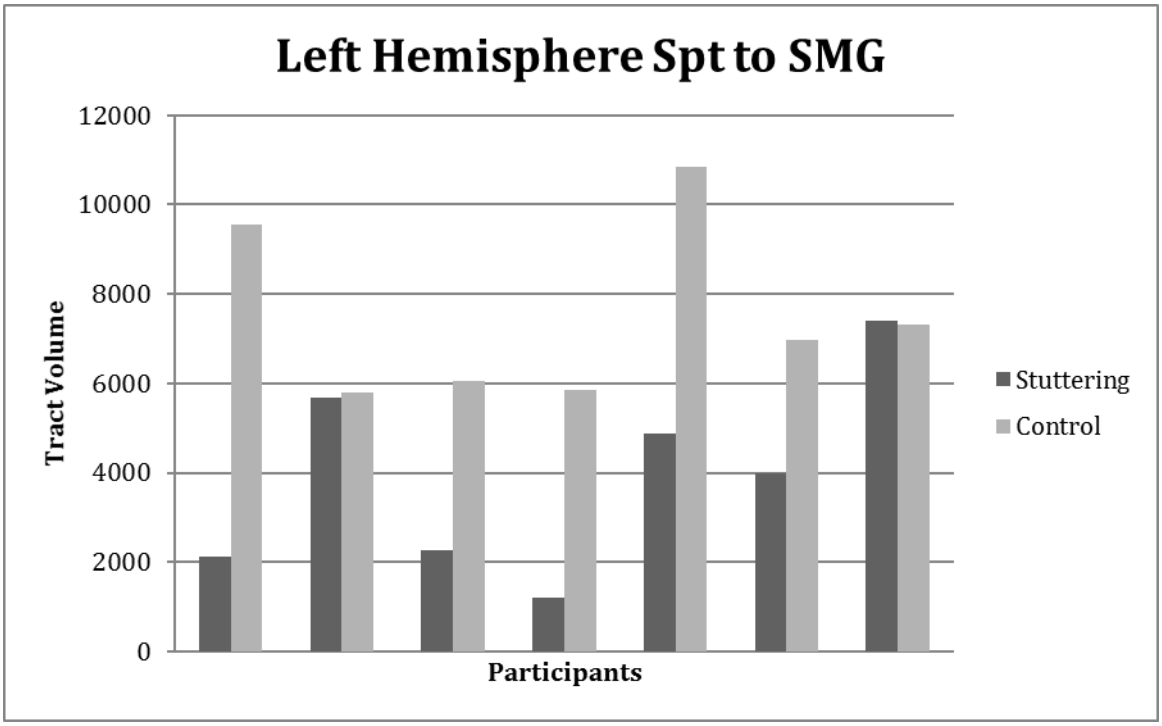


Figure 17: Tract volume comparisons of left hemisphere Sylvian parietal temporal region (Spt) and Supramarginal Gyrus (SMG) between participants who stutter and participants who do not stutter. The comparisons are age and sex matched between the groups

Analyses of the left hemisphere also revealed reduced white matter volume tracts connecting the Spt and RO in people who stutter when compared to people who do not stutter (Figure 18). Spt-RO is an important feedback pathway that connects the auditory translator (Spt) to a frontal region associated with articulation (RO). Activity in RO is associated with lingual, laryngeal and pharyngeal movement (Brown et al., 2008). RO contains sensorimotor representations of the articulatory muscles (Brown et al., 2009). Findings of this study substantiate previous evidence of decreased FA of white matter surrounding RO and delayed activation of RO in people who stutter (Biermann-Ruben et al., 2005; Sommer et al., 2002). Sensorimotor theories have postulated that a deficient Spt can result in incorrect sensory predictions, leading to generation of incorrect error signals. The repeated attempts to correct the

incorrect error signals are said to result in sound syllable repetitions (Hickok et al., 2011). Evidence from neuroimaging studies corroborates the implication of the Spt in stuttering. In addition, neurons in the Spt have been shown to activate for vocal tract movements not specific to speech and are responsive to both motor and sensory stimuli (Hickok et al., 2009). Decreased connectivity between the Spt and RO seen in this study lends support to the hypothesis that stuttering could result from a deficiency in the feedback commands from the Spt to cells in the feedforward region RO. In addition, a negative correlation was noted between the QA of the left Spt-RO and OASES-A scores, and volume of the tract and overall score on SSI-4. This indicates a possible relationship between white matter integrity and stuttering severity. The functional and structural neuroimaging evidence of atypical activation in RO combined with the findings of this study of reduced white matter integrity is suggestive of a possible weak link in the information transfer between auditory-motor integrator (Spt) and feedforward motor effector (RO) in people who stutter.

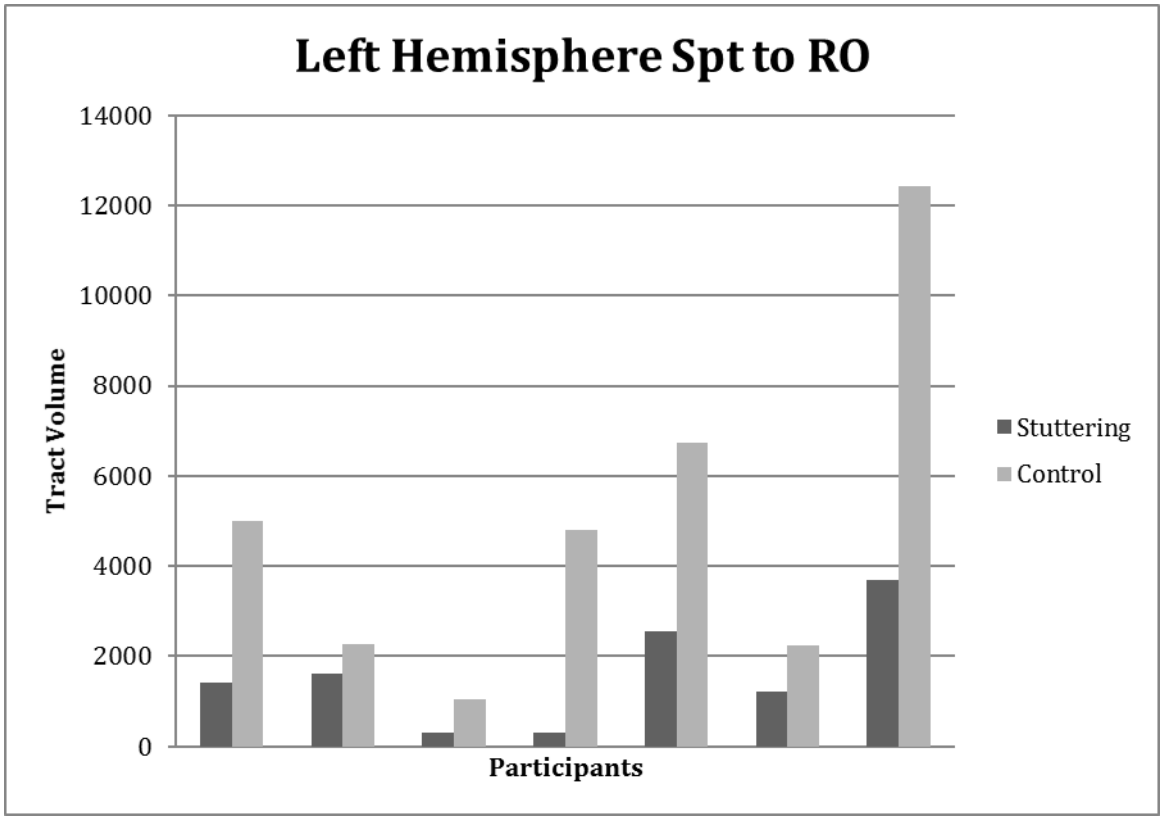


Figure 18: Tract volume comparisons of left hemisphere Sylvian parietal temporal region (Spt) and rolandic operculum (RO) between participants who stutter and participants who so not stutter. The comparisons are age and sex matched between the groups

5.1.1.2 Right hemisphere comparisons

Analyses of the right hemisphere revealed reduced white matter volume in the tract connecting the Spt to HG in people who stutter when compared to people who do not stutter (Figure 19). This finding is inconsistent with the second hypothesis that people who stutter will show increased white matter integrity in the right hemisphere. HG is involved in early processing of auditory stimuli, and neurons in the HG are suppressed when people hear their own voice (Hickok, 2001; Rauschecker, 2011; Salmelin, 2007). Increased bilateral activations of the HG

have been noted in people who stutter (Chang et al., 2009; Loucks et al., 2011). Interestingly, fluency enhancing strategies such as choral reading have been noted to eliminate atypical right lateralized over-activation in motor areas and to reduce activation in right auditory regions, suggesting a compensatory role for the right hemisphere (Fox et al., 1996; Fox et al., 2000; Neumann et al., 2003). Reduced tract volume in the HG-Spt tract could be the result of compensatory strategies, as all the participants reported diagnosis of developmental stuttering. Further investigations into the neural activations following treatment are necessary to explore the compensatory role of the right hemisphere.

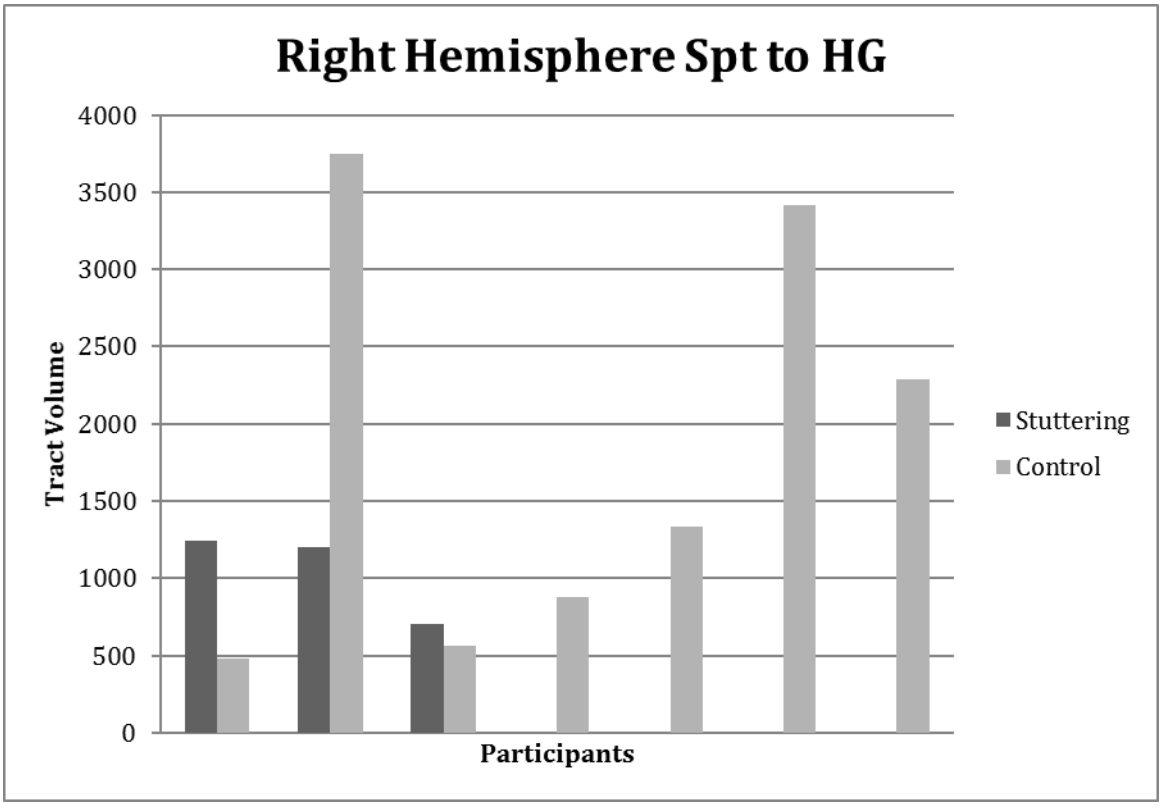


Figure 19: Tract volume comparisons of right hemisphere Sylvian parietal temporal region (Spt) and Heschl's Gyrus (HG) between stuttering and control group participants. The comparisons are age and sex matched between the groups

5.1.2 FA

Significantly reduced FA was also seen in people who stutter compared to people who do not stutter in the left RO-PM tract (Figure 20). PM is postulated to integrate expected sensory targets with specific motor output (Ghosh et al., 2008). Ventral left PM region is hypothesized to be the Feedforward Control Map according to the DIVA model (Tourville et al., 2008). The Feedforward Control Map is said to receive temporal information of a particular speech sound from the speech sound map and converts the information into motor programs of that particular speech sound. Projections from the Feedforward Control Map to bilateral motor cortex transform the motor programs into motor commands required to produce the sound. Activations in both RO and PM are seen during speech production (Behroozmand et al., 2015). Considering the importance of both PM and RO in speech production, a decrease in FA in the RO-PM tract may result in slower integration of information in the feedforward loop (Tourville & Guenther, 2011). Because FA, which is an indirect measure of myelination, is related to speed of information processing and transfer (Yeh et al., 2016), a reduction in FA could possibly contribute to atypical functional and temporal activations of RO and PM cortex seen in people who stutter (Chang et al., 2009; Loucks et al., 2011; Salmelin et al., 2000; Watkins et al., 2008).

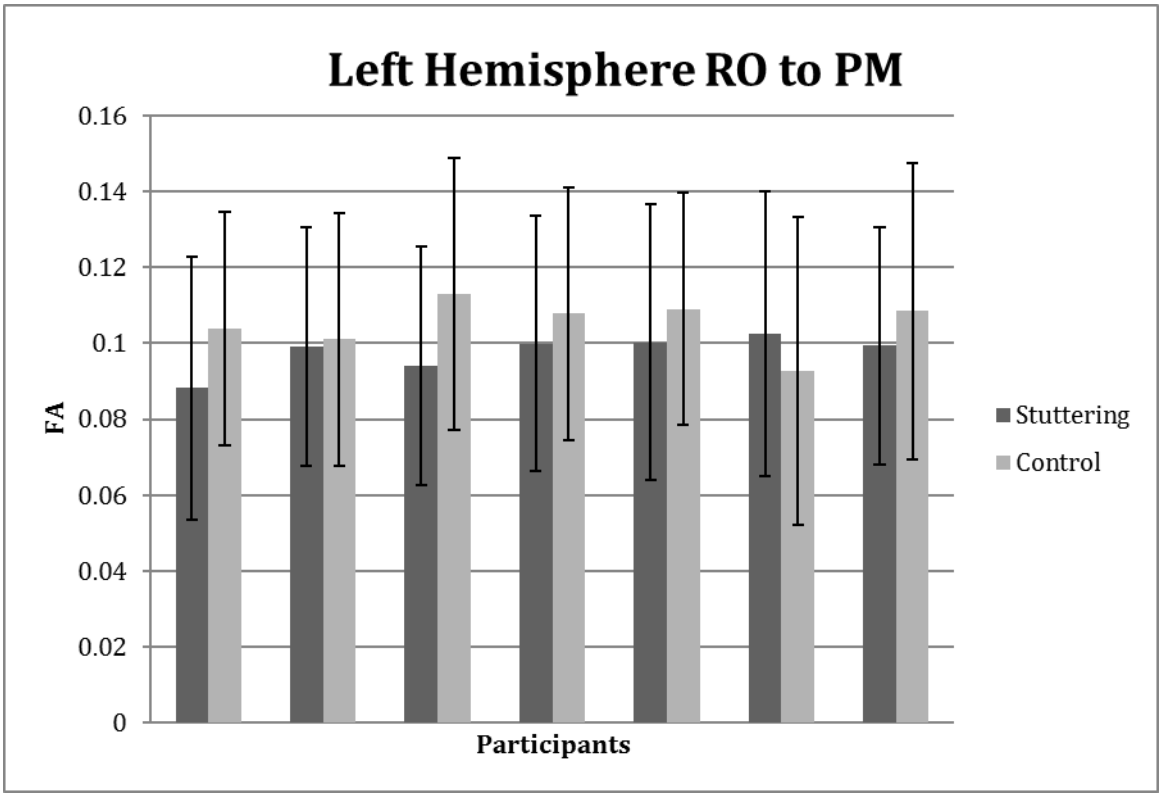


Figure 20: FA comparisons of right hemisphere rolandic operculum (RO) to premotor (PM) tract between stuttering and control group. Comparisons shown are age and sex matched between groups

Interestingly, results of this study did not find significant differences in QA of the tracts segmented between people who stutter and those who do not. A possible explanation for this lack of difference could be attributed to the metric used to assess the difference. Lower QA represents the density or cohesiveness of the fiber bundles (Yeh et al., 2016), whereas a decrease in volume and FA is representative of neuro-degeneration and demyelination, respectively. In addition, the absence of differences in the white matter integrity of tracts connecting the IFG to other sensorimotor regions is inconsistent with previous research. Decreased functional activation of the left IFG and increased activation of the right homolog of IFG were noted in people who stutter when compared to people who do not stutter (Chang et al., 2009; Loucks et al., 2011).

Despite the functional activation differences, only one study found higher white matter volume surrounding the right IFG in people who stutter when compared to people who do not stutter (Jäncke et al., 2004). It is possible that the methodology used in this study contributed to the results: Jäncke and colleagues used voxel-based morphometry, while this study used the HDFT approach. Voxel-based morphometry investigates focal differences in brain anatomy, while HDFT focuses on mapping entire tracts. Conversely, it is possible the atypical activation of the left IFG is due to a deficiency in an indirect connection in the sensorimotor network. For example, significantly lower tract volume of the left RO-PM was found in people who stutter when compared people who do not stutter. IFG is functionally and structurally connected to PM. A weak connection to the PM could possibly affect activation of IFG. This possibility should be further investigated by combining structural with functional neuroimaging studies.

5.2 CORRELATION BETWEEN QA OF TRACTS AND SEVERITY AND IMPACT SCORES

5.2.1 Correlation between QA and OASES-A

Results of correlation analyses supported the hypothesis that stuttering severity scores would be negatively correlated to QA of tracts connecting the ROIs. The analysis revealed a significant negative relationship between QA of the left Spt-RO and the impact of stuttering as measured by the OASES-A (figure 10). A significant negative relationship between tract volume of the left Spt-RO and stuttering severity as measured by the SSI-4 was also noted. The relationship

between Spt and RO is of particular interest since the volume of this tract was lower in people who stutter when compared to those who do not, indicating a reduction in information transfer between feedback and feedforward circuits. The correlation between behavioral data and QA of the tract indicates that the interaction could possibly be associated with stuttering. It is possible that stuttering is not only attributed to a deficiency in feedforward system but also a weak interaction between the feedforward and feedback circuits.

Similar negative correlations were seen between OASES-A scores and QA of tracts the right IFG-RO (Figure 11) and the right RO-PM (Figure 12). Right hemisphere frontal regions have been noted in altered auditory feedback conditions (Ghosh et al., 2008). Specifically, right IFG and PM are postulated to be the feedback control maps and have shown to activate during error correction in altered feedback conditions (Golfinopoulos et al., 2011; Tourville et al., 2008). Activation in the right hemisphere was also noted in the right RO in people who stutter during a sentence production. This activation was absent in people who do not stutter. In addition, activation in the left RO was decreased in people who stutter compared to people who do not stutter (Biermann-Ruben et al., 2005). This evidence, combined with the findings of this study of lower FA of the left RO-PM, lends support to the assertion that right hemisphere activations are compensatory. It is possible that the right hemisphere was recruited to compensate for weak feedforward circuit but the right hemisphere activation was not strong enough to overcome stuttering (Travis, 1978; Yeh et al., 2016).

5.2.2 Correlation between QA and SSI-4

A significant negative relationship was noted between overt stuttering severity measured by SSI-4 and QA of left IFG-HG and IFG-SMG and right IFG-Spt and IFG-PM in people who stutter. These correlations indicate a negative relationship between overt stuttering behaviors and QA of pathways involved in sensorimotor integration. Notably, connections to the IFG showed a significant negative correlation with SSI-4 scores. This significant correlation was seen even with the limited stuttering severity rating. Left IFG is said to be involved with articulatory control and phonetic coding (Bhatnagar, 2002; Guenther, 2006), and it serves as the Speech Sound Map in the DIVA model (Tourville et al., 2008). According to the model, projections from the speech sound map are said to activate expected auditory and somatosensory targets. In addition, prior studies have shown that decreased activation of the left IFG is associated with stuttering during overt reading tasks (Brown et al., 2005; Chang et al., 2009; Loucks et al., 2011). Activation of the left IFG was noted during normal feedback conditions. Therefore, it is not surprising that connections to the left IFG to auditory and somatosensory regions are correlated with stuttering severity. The right IFG on the other hand is considered to be the Feedback Control Map according to the DIVA model and is activated during tasks involving altered auditory feedback (Ghosh et al., 2008; Tourville et al., 2008). Altered auditory feedback has been shown to induce fluency in people who stutter (Kalinowski, Stuart, Sark, & Armson, 1996; Stuart, Kalinowski, Rastatter, & Lynch, 2002) and the right IFG activates for altered feedback it can be deduced that the right hemisphere plays a compensatory role. Then the significant negative correlation between stuttering and the right IFG-Spt and IFG-PM seen in this study adds support to existing evidence regarding the role of the right hemisphere in people who

stutter. Interestingly, white matter measures did not reveal any significant differences in these tracts between the two groups. This inconsistency could be attributed to the limited stuttering severity range due to a small sample. Conversely, considering the limited severity range of stuttering and the absence of significant white matter integrity differences, it is possible that the QA of the connections to IFG are correlated with speech production and not stuttering.

In summary, pathways that connect sensorimotor regions such as the left IFG, PM, Spt, HG, SMG, and RO were negatively correlated with SSI-4, indicating sensorimotor involvement. These results are consistent with previous findings that indicate negative correlation between stuttering severity and white matter connection between left mid-motor cortex and the ventral motor cortex (Cai et al., 2014). Significant correlations between impact scores on the OASES –A and the right hemisphere tracts: RO-PM and IFG-RO, seen in this study, support the hypothesis that the right hemisphere frontal regions are activated to compensate for a weak feedforward commands (Ghosh et al., 2008; Tourville et al., 2008). The only tract that was lower in white matter integrity and negatively correlated with stuttering severity and impact scores was the left Spt-RO. This indicates a possible inefficiency in expected auditory predictions resulting in incorrect error generation. None of the other tracts with reduced white matter integrity correlated with stuttering severity. The lack of a more widespread relationship between white matter integrity differences and stuttering severity could be attributed to the possibility that people who stutter recruit different neural processes to compensate for a deficient sensorimotor system. Conversely, people who stutter might recruit the same processes, as people who do not stutter but the compensatory activations are not strong enough to overcome stuttering. Another plausible explanation for lack of correlation could be the limited severity range exhibited by the participants who stutter.

Correlations of OASES-A to white matter integrity should be further investigated within the framework of multifactorial theories of stuttering. For example, Smith and Kelly, 1997 proposed a Unified Approach to Stuttering, which suggests that several factors contribute to the development of stuttering such as emotional, sociocultural, cognition, and psychological factors, but in order to play a role in stuttering each of these factors must adversely affect the speech production system. Because OASES-A is a self-report assessment of affective, cognitive and behavioral reactions of people who stutter towards stuttering, it targets some of the factors that might affect the speech production system. As connectivity between brain regions involved in cognitive and affective functions were not assessed in this study, future investigations should examine the relationship of these reactions to speech production neural network.

5.3 LIMITATIONS AND FUTURE DIRECTIONS

Although HDFT provides a more accurate and better visualization of the white matter tracts than DTI studies, it should be noted that functional or effective connectivity should not be deduced from structural connectivity. The results of this study reveal possible weakness in the sensorimotor network and should be interpreted in conjunction with functional activation studies. The direction of information flow of information in the tracts cannot be determined from this study. The seed and end ROIs were chosen arbitrarily because the functional and effective connectivity between all the ROIs has not yet been investigated. For example, the functional activation of Spt has not yet been examined in people who stutter. Another potential factor that could have influenced the outcomes is the limited range of severity in stuttering among the

participants. The limited severity range of very mild-to-mild range can be attributed to the small sample size. Even though the sample size was based on an effect size reported in Cai et al (2014), it was not large enough to recruit participants with a wider range of stuttering severity. In addition, the small sample size led to a sampling bias as all the participants had received therapy in the past and were involved in self-help groups. However, the overall impact score from OASES-A ranged from mild to moderate indicating a discrepancy between self-report and objective measures. This discrepancy can be attributed to the day-to-day variability seen in stuttering. Despite this limitation, a significant correlation was found between severity scores and QA of some of the tracts connecting sensorimotor regions. Therefore, it can be deduced that there is a correlation between the QA of tracts and stuttering severity scores but the strength of the correlations should be interpreted with caution.

In addition, the study did not examine the connectivity between other regions involved in speech production such as motor cortex, cerebellum, or the basal ganglia. Cerebellum is said to be involved in the sequencing of syllables required for speech (Ackermann, 2008). Pre-treatment assessments indicated higher right cerebellar activations during overt speaking tasks in people who stutter when compared to people who do not stutter. Immediately post-treatment the activations in the right cerebellum were larger compared to baseline but decreased to levels closer to those who do not stutter at the one-year follow-up (De Nil et al., 2001). Similarly, the basal ganglia have been suggested to be involved in spatial and temporal cues for the syllables. Stuttering has been attributed to an impaired basal ganglia to provide correct temporal cues for initiation of speech (Alm, 2004). Therefore, it is important to examine the connectivity of these sub-cortical structures to cortical structures.

Technological advances have made it possible to examine brain pathways using non-invasive, efficient approaches. However, the quantification of the pathways is still evolving. To date there isn't a gold standard for quantifying white matter integrity, mainly due to the variability of cortical folding. This makes it difficult to identify anomalies associated with disorders such as stuttering. However, using a sex- and age-matched group of people who do not stutter as control validates the results of this study. The results of this study provide the foundation for replication in a larger sample

Since structural connectivity does not imply functional or effective connectivity, follow-up studies should investigate the relationship between structure and function. In addition, since connectivity of subcortical regions plays an important role in speech production, pathways between cortical and subcortical regions will be assessed. Future studies include:

1) Investigating temporal activation differences between sensorimotor regions to substantiate structural differences using MEG. Stuttering has been attributed to a mismatch in timing between the linguistic and motor loop (Foundas, Bollich, et al., 2004). Support from this assertion comes from temporal activation studies that showed delayed activation in RO in people who stutter when compared to people who do not stutter. Sustained right rolandic operculum activation up to 800 ms in word repetition task was also seen only in people who stutter. There was also delayed activation of left inferior frontal cortex in people who stutter from 95 to 145 ms which was not noticeable in control subjects (Biermann-Ruben et al., 2005; Salmelin et al., 2000). However, very few studies have combined technologies to validate the structural connectivity of the auditory motor network with functional connectivity studies. Combining information obtained from complementary technologies will lead to a comprehensive understanding into the neurological underpinnings of stuttering.

2) Examining white matter integrity of tracts that connect the primary motor cortex and cerebellum to PM and IFG. Cerebellum is postulated to be involved in motor learning and sequences of syllables (Ackermann, 2008). Increased left cerebellar activation and decreased FA surrounding cerebellum bilaterally was found in people who stutter (Brown et al., 2005; Chang et al., 2009; Watkins et al., 2008). Primary motor cortex is functionally connected to the PM and IFG, areas that are atypically activated in people who stutter (Loucks et al., 2011; Tourville & Guenther, 2011). Increased white matter volume of the left PM, IFG and primary motor cortex have also been noted in people who stutter (Jäncke et al., 2004). Assessing the white matter integrity of tracts connecting the primary motor and cerebellum to other sensorimotor regions will be another piece that will add to the understanding of the neurological basis of stuttering.

3) Replicating results from this dissertation study in a larger sample to increase power so results can be generalized. A larger sample will allow for the recruitment of participants with a wider range of stuttering severity and offer more power so the results can be generalized. It will also allow for stringent measures to control type 1 errors.

4) Assessing structural differences between hemispheres in people who stutter to understand right hemisphere's role in stuttering. Although people who stutter exhibit widespread atypical activation, three neural signatures emerge: consistent increased activation in the right frontal operculum/anterior insula; increased activation in cerebellar areas and decreased activation in the auditory areas bilaterally (Brown et al., 2005). More recent studies have generally seen an increase in right hemisphere activation and decrease in left hemisphere activation in people who stutter when compared to people who do not stutter. Comparing hemispheric differences will help to understand the role of the right hemisphere in stuttering.

5) Investigating functional activation differences of the ROIs: PM, Spt, SMG, PM, HG, primary motor cortex and cerebellum between people who stutter and those who do not. To add support to the findings of the current study, strength of activation will be correlated to the white matter integrity measures.

6) Examining the extent of interaction between sensory systems during speech production by comparing behavioral data to neural activations. Behavioral data shows that people who stutter process sensory information differently than people who do not stutter (De Nil & Abbs, 1991; Loucks & De Nil, 2012). For example, fluency is temporarily increased during singing or choral reading in some people who stutter. Delayed or altered auditory feedback has also shown to temporarily induce fluency in people who stutter. Similarly, people who stutter exhibit slightly delayed response time in finger tapping tasks. Evidence also suggests a negative correlation between compensation for auditory perturbation and somatosensory perturbation. The relationship between white matter measures and behavioral data will be examined to determine the interaction between the sensory modalities.

7) Investigating structural anomalies in children who stutter to determine if differences in white matter integrity cause stuttering or if they are a result of stuttering. Most of the evidence for the neurological basis for stuttering comes from studies investigating adults who stutter. The primary question that arises with these studies is whether the atypical activations are compensation for stuttering or if they cause stuttering. Very few studies have examined neural differences in children who stutter mainly because of the time intensive neuroimaging procedures. With the advance in technology, the scanning time for HDFT approach has been decreased to 20 minutes. This makes it possible to study children who stutter as close to the onset of stuttering as possible.

6.0 CONCLUSION

White matter connectivity between sensorimotor regions in people who stutter was compared with those in who not stutter using HDFT. Three robust measures, white matter volume, FA and QA, were calculated to assess the integrity of fibers. White matter volume is correlated to the intra-cellular liquid in the axons. Decreased volume is indicative of neuro-degeneration, which results in loss of amount of information transmitted. FA represents water diffusion in a voxel and is representative of the myelination of the axons. The amount of myelin coating an axon represents the speed of information transfer. QA is a measure of water diffusion along the axon representing the cohesiveness of the fiber bundle. Correlations between QA and both stuttering severity and impact were calculated to assess the links between behavioral and neurological data.

Results of this study indicate that people who stutter exhibited decreased tract volume in left hemisphere connections of Spt to RO and SMG, and RO to PM. Spt is hypothesized to be the auditory motor translator and stuttering has been attributed to a "noisy" translator (Hickok et al., 2011). Evidence also suggests that neurons in Spt activate for both auditory and motor tasks more specifically for laryngeal elevation. In addition, activation in Spt is higher for subvocal rehearsal than for continuous listening indicating selectiveness for the motor modality (Hickok et al., 2011(Hickok, 2009 #78). Neuroimaging evidence also indicates that RO is also involved in laryngeal elevation (Brown et al., 2005; Brown et al., 2008). A decrease in the connections

between Spt and RO in people who stutter denotes a weak link in the feedback Spt and frontal sensorimotor region RO, both regions involved in laryngeal elevation. The negative correlation between OASES-A, a self-report of impact of life and connections to Spt could be attributed to the sub-vocalization that might happen before and during speaking in a person who stutters. A section of the OASES-A reflects the speaker's experience before and during stuttering. Negative correlation between SSI-4 and Spt-RO was also noted in people who stutter. The SSI-4 measures stuttering severity from the listener's perception and does not include the events preceding audition, such as a block. Therefore, the SSI-4 mostly measures stuttering events during and after speech production. It can be deduced that OASES includes an indirect measure of stuttering before it occurs. The correlation data when combined with reduced tract volume points to a dissociation between laryngeal movement before and during speech production. More behavioral investigations into the laryngeal movement in people who stutter are necessary to substantiate the dissociation.

Decreased connections between Spt and SMG indicate weak wiring between somatosensory and auditory feedback regions suggesting an inadequate gating mechanism between the sensory systems. Evidence points to a negative correlation between compensation for auditory perturbation and compensation for somatosensory perturbation. This suggests an interaction between the two sensory systems. In addition, both Spt and SMG are hypothesized to be the sensory error and target maps in the DIVA model (Tourville & Guenther, 2011). The error maps are inverse target maps and any input to this area results in inhibition of expected sensory feedback for the target sound. Reduced tract volume connecting these areas could result in decrease information transfer between the two systems leading to activation of both systems to compensate for perturbation such as those seen with stuttering. In addition, according to the

Hierarchical State Feedback Model, auditory feedback is involved in the higher-level linguistic units and somatosensory feedback is involved in lower-level phonemic units (Hickok et al., 2011). The interaction between the two feedback systems is complex and varies based on the sounds produced. Therefore, weak connections between the regions involved in sensory feedback could lead to lack of inhibition of one sensory modality in favor of feedback from preferred sensory modality resulting in interference from non-preferred modality.

Reduced FA was also noted in white matter connections of left RO to PM in people who stutter when compared to people who do not stutter. According to the DIVA model, PM is responsible for receiving temporal information, converting the information into motor programs and transmitting the programs to the speech sound map, where the programs are transformed to speech commands. The speech commands are then transmitted to the muscles for articulation. As noted before, activations in the RO are noted with articulation. Decreased FA in the connections between these regions could result in temporal delays in transmission of muscle commands to the articulators. This finding substantiates temporal activation delays in left RO in people who stutter.

Negative correlations were noted between SSI-4, a stuttering severity measure based on the auditory perception of the listener, and bilateral connections to IFG. SSI-4 measures the stuttering event from the time the stutter is visible or audible to the listener. IFG is suggested to be involved in articulatory control, syllabification and assembling articulatory codes (Bhatnagar, 2002; Tourville & Guenther, 2011). In addition, reduced functional activation has been noted in left IFG in people who stutter when compared to people who do not stutter. IFG is also hypothesized to be the neural correlate of speech sound map, where muscle commands are

transmitted to articulators. Because IFG is involved in overt articulation, a negative correlation between SSI-4 and connections of IFG is not surprising.

In sum, the results extend previous research by mapping connectivity between sensorimotor regions that are atypically activated in people who stutter during speech production. Specifically, white matter integrity of connections of the left Spt and RO was decreased in people who stutter when compared to people who do not stutter. Both Spt and RO are regions that are involved in laryngeal elevation, opening up the possibility of atypical laryngeal movement in people who stutter.

Another important finding is the reduced tract volume between the somatosensory (SMG) and auditory feedback regions (Spt), which indicates weak gating mechanism between the sensory modalities. The non-preference for a sensory modality to compensate for stuttering could result in repeated error corrections in order to match the target sensory output to expected sensory output.

The negative correlations between stuttering severity measures and impact on life to white matter integrity point to dissociation between laryngeal movements before and during speaking in a person who stutters. Further investigations are necessary to examine relationship between speaker's experience and white matter integrity.

APPENDIX A

BACKGROUND INFORMATION FORM (People who stutter)

1. How old are you?
   Age range must be between 21-40

2. Sex: _____Male _____Female
   If female, are you pregnant?

3. Age of onset_____

4. Age of diagnosis of stuttering _____

5. Have you had therapy for Stuttering?
   If yes, how long?

6. Are you currently receiving therapy for stuttering?

7. Handedness:
   Are you Left handed _____ Right handed_____

MRI clearance

1. Have you had an MRI before? Yes No

2. Are you claustrophobic? Yes No

3. Weight _____

Background Information Form (control group)

1. How old are you?

Age range must be between 21-40

2. Sex: _____Male _____Female

3. Do you stutter presently?

4. Have you ever stuttered?

5. Have you ever received speech language therapy?

If Yes, for what?

When?

7. Handedness:

Are you left handed _____ Right handed _____

MRI clearance:

1. Have you had an MRI before? Yes No

2. Are you claustrophobic? Yes No

3. Weight _____

4. Height _____

CONSENT TO BE A SUBJECT IN A RESEACH STUDY (People who stutter)

Identifying neuroanatomical differences in people who stutter using High Definition Fiber Tracking

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Co-Investigator: Sudhir Pathak
Programmer
Dr. Schneider's Laboratory
Department of Bioengineering
(412)-624-7063

Sources of Support: National Stuttering Association

Please read the entire consent form carefully so you fully understand the procedures and assessments you will undergo as part of this study.

Purpose of the study:

The objective of this study is to examine the pathways between brain regions involved in speech production in people who stutter. This study will use a cutting edge approach that will result in better visualization of connections between speech related brain regions.

Participant eligibility:

This pilot project will examine MRI scans of seven people (1 per person) who stutter to understand the neural underpinnings of stuttering. Participants will go through the assessments and procedures specified in the following sections. Stuttering diagnosis will be based on self-report and confirmed by a licensed speech language pathologist. Subjects who report that they are pregnant will be excluded from the study.

Procedures of the study:

1) Overall Assessment of the Speaker's Experience of Stuttering (OASES)

OASES measures the impact of stuttering on a person's day to day activities. It is a questionnaire-based self-assessment of the speaker's perception of stuttering behaviors. Administration time is estimated to be less than 20 minutes. This measure is used to assess the speaker's perception of his/her speaking.

2) Stuttering Severity Instrument- 4th Edition (SSI 4)

SSI 4 is a stuttering severity measurement based on frequency, duration and secondary behaviors. The SSI is a paper and pencil test based on a 15-minute conversation with the participant. The conversation will be video recorded. Administration time is estimated to less than 20 minutes. Scores from this test will be correlated with the structural imaging data. Scores for the test will not be used for eligibility purposes.

3) Hearing screening. The screening will take 5 minutes and is done to assess auditory acuity of participants.

4) Dichotic Words Test: The test will take 10 minutes. The test will be administered in the sound booth in Dr. Moncrieff's lab.

5) Randomized Dichotic Digit Test: The test will take 5 minutes and will be administered in the sound booth in Dr. Moncrieff's lab

6) Dichotic Syllable Test: The test will take 5 minutes and will be administered in the sound booth in Dr. Moncrieff's lab

7) Magnetic Resonance Imaging (MRI)

Participants will complete brain-imaging procedures that will be carried out at the Magnetic Resonance Research Center on the 8th floor of UPMC Presbyterian by trained technicians.

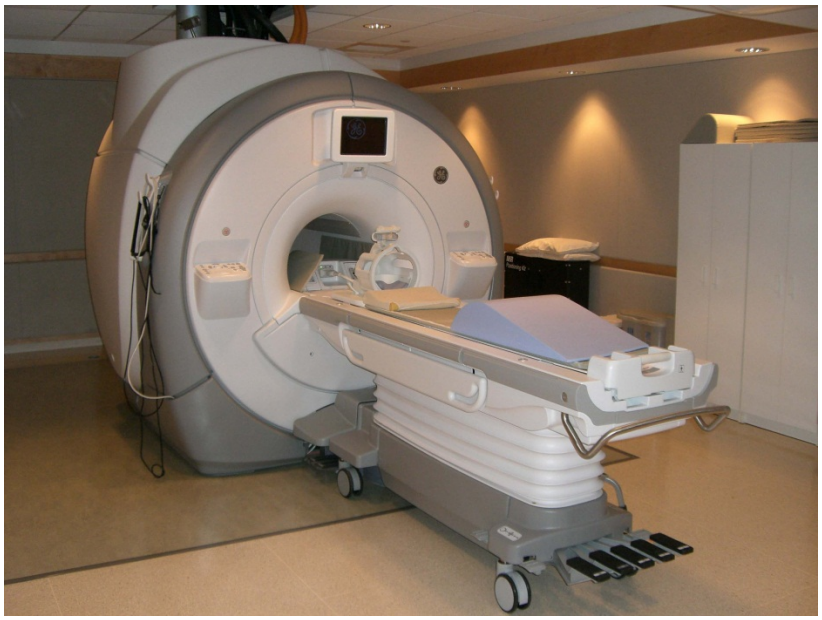
Scientists use MRI to create images of the brain from magnetic signals, and this particular MRI involves additional sequences that create high definition images of nerve fibers. The MRI involves lying on a table that moves into a hollow machine (the magnet). Each MRI examination requires approximately one hour, during which time you will be asked to lie still. While the scanner is operating, you may hear a noise similar to someone knocking loudly and rapidly on a metal door. You will always be able to talk with the operator or technologist during the study. We will place pads to help you keep comfortable and still.

Tasks to be performed during the MRI scanning:

a) dMRI: lying on the table – no task (35minutes)

b) fMRI: the participants will name pictures and repeat words while lying on the table (25 minutes)

Because of the powerful magnet used in MRI, metal objects within your body could move, and this movement could result in your injury. Based on the medical or occupational history that you will provide during screening, there is a possibility that some foreign metal object(s) may be present in your body or around your eyes. Participants with metal objects in their body will be excluded from the study.



Possible risks, side effects and discomforts of participation in this study:

During the MRI exam, the subject will be exposed to a magnetic field. This magnetic field does not include exposure to x-rays or radioactivity. For safety, the subject will be asked about any internal magnetic objects, such as pacemakers or other implants. In the event that he/she does have any magnetic objects, he/she will not be permitted to continue with the study procedures. The subjects will be asked to remove all personal metallic objects and they will be placed in a locker outside the magnet room. During the scan, the magnet will make intermittent, loud knocking sounds that could cause discomfort for some people. To minimize this potential discomfort, the subject will be asked to wear earplugs. The earplugs will not interfere with the

subject's ability to communicate with the magnet operator. Additionally, some people might feel claustrophobic in the magnet, and if this is the case the study can be ended early.

While all information about the subject's participation in this research will be handled in a confidential manner, a breach of confidentiality is another potential risk present in this study. All data collected during the procedures of this study will be labeled only with an assigned research code number; and only certified members of the research team will have access to the identity of any participant.

Although there are no known risks for pregnant women to go through a MRI procedure, we will exclude women who are pregnant for this study.

Although the MRI scans are conducted to answer research questions; there is a possibility that we may detect something unusual or different within your results. In this unlikely event, the neurosurgeon or neuropsychologist will discuss these findings with you. The results of the research MRI will not become part of the subject's hospital record.

Another possible risk to the participant is testing fatigue during behavioral testing. The participant will be given frequent breaks during the behavioral testing to overcome testing fatigue.

Benefits of Participation:

There is no direct benefit for participating in this study. This study will provide a better understanding the neural signatures of stuttering eventually leading to individualized treatment plans.

Compensation for participating in the study:

None of the procedures described in this protocol are performed as a part of standard clinical care, and no third party providers (insurance companies) will be charged for any of these procedures. Participants will be paid $50.00 for completing research study.

Compensation for injury as a result of taking part in the study:

University of Pittsburgh researchers and associates will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please immediately contact the principal investigator listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Data acquisition and management:

All identifiable records and data will be kept confidential, in locked files and password protected computer files. These files are only accessible to researchers involved in the study. The records will be de-identified by using a case number. The de-identified records will be maintained in a separate location for a minimum of seven years.

Disclosure of identifiable medical information:

Medical information will not be used in this research study. The information obtained as part of the study (MRI scans) will be used for understanding the neurological basis of stuttering. All information acquired as part of the study will be maintained with utmost confidentiality. The information will not be accessible to third party, including relatives, insurance companies or other researchers except with a few exceptions mentioned in the following section.

Access to identifiable information:

Investigators listed on the first page of this consent form will have access to your identifiable information. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable information for the purpose of monitoring the appropriate conduct of this research study.

Voluntary participation:

Participation in this study is completely voluntary and you have the right to withdraw from participation at any time and for any reason. If you do decide to withdraw, all data acquired up until that point in the study would be retained for use in our analysis.

Questions about the study:

If you have any questions about the study please contact the principal investigators listed on the first page of this form. Questions about your rights as a research participant can be directed to Human Subjects Protection Advocate at the University of Pittsburgh IRB Office, 1-866-212-2668.

VOLUNTARY CONSENT

• I have read the consent form for this study and any questions I had, including explanation of all terminology, have been answered to my satisfaction. A copy of this consent form will be provided to me.

• I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that those questions will be answered by the researchers listed on the first page of this form.

• I understand that my participation in this study is voluntary and that I am free to refuse to participate or to withdraw my consent and discontinue my participation in this study at any time without affecting my future relationship with this institution.

• I agree to participate in this study.

_____	_____	_____
Date & Time	Subject's Signature	Subject's Printed Name

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date/Time

CONSENT TO BE A SUBJECT IN A RESEACH STUDY (Control group)

Identifying neuroanatomical differences in people who stutter using High Definition Fiber Tracking

Principal Investigator: Sujini Ramachandar, MS, CCC-SLP
University of Pittsburgh
6073 Forbes Tower
Pittsburgh, PA 15260
(315)-263-0861

Mentor/Advisor: Dr. Scott Yaruss, Ph.D., CCC-SLP, BRS-FD
University of Pittsburgh
6073 Forbes Tower
Pittsburgh, PA 15260
(412) 383-6538

Co-Investigator: Sudhir Pathak
Programmer
Dr. Schneider's Laboratory
Department of Bioengineering
(412)-624-7063

Sources of Support: National Stuttering Association

Please read the entire consent form carefully so you fully understand the procedures and assessments you will undergo as part of this study.

Purpose of the study:

The objective of this study is to examine the pathways between brain regions involved in speech production in people who stutter. This study will use a cutting edge approach that will result in better visualization of connections between speech related brain regions.

Participant eligibility:

Control Group: For the control group we will be recruiting seven people who do not stutter. Absence of stuttering will be confirmed by self -report. Participants will go through the assessments and procedures specified in the following sections.

Procedures of the study:

1) Magnetic Resonance Imaging (MRI)

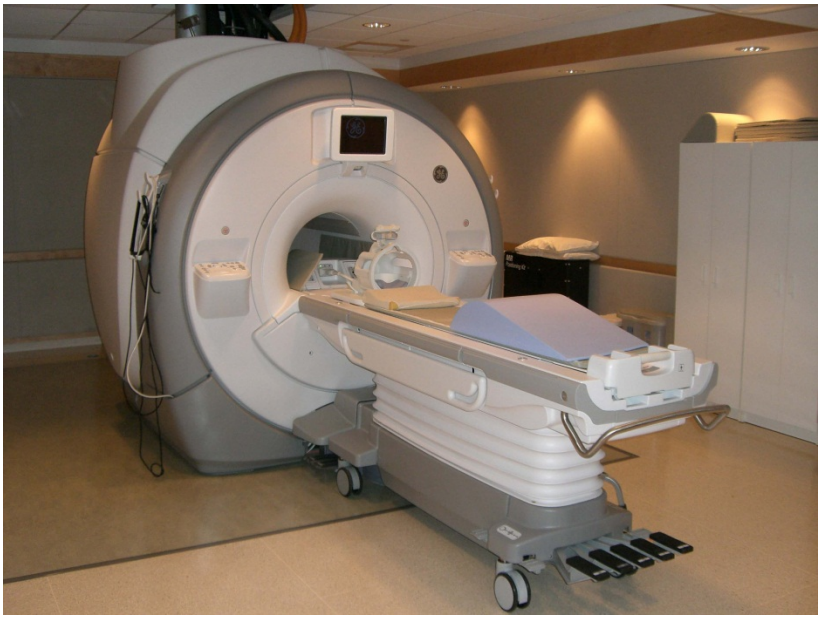
Participants will complete brain-imaging procedures that will be carried out at the Magnetic Resonance Research Center on the 8th floor of UPMC Presbyterian by trained technicians. Scientists use MRI to create images of the brain from magnetic signals, and this particular MRI involves additional sequences that create high definition images of nerve fibers. The MRI involves lying on a table that moves into a hollow machine (the magnet). Each MRI examination requires approximately one hour, during which time you will be asked to lie still. While the scanner is operating, you may hear a noise similar to someone knocking loudly and rapidly on a metal door. You will always be able to talk with the operator or technologist during the study. We will place pads to help you keep comfortable and still.

Tasks to be performed during the MRI scanning:

a) dMRI: lying on the table – no task (35minutes)

b) fMRI: the participants will name pictures and repeat words while lying on the table (25 minutes)

Because of the powerful magnet used in MRI, metal objects within your body could move, and this movement could result in your injury. Based on the medical or occupational history that you will provide during screening, there is a possibility that some foreign metal object(s) may be present in your body or around your eyes. Participants with metal objects in their body will be excluded from the study.



Possible risks, side effects and discomforts of participation in this study:

During the MRI exam, the subject will be exposed to a magnetic field. This magnetic field does not include exposure to x-rays or radioactivity. For safety, the subject will be asked about any internal magnetic objects, such as pacemakers or other implants. In the event that he/she does have any magnetic objects, he/she will not be permitted to continue with the study procedures. The subjects will be asked to remove all personal metallic objects and they will be placed in a locker outside the magnet room. During the scan, the magnet will make intermittent, loud knocking sounds that could cause discomfort for some people. To minimize this potential discomfort, the subject will be asked to wear earplugs. The earplugs will not interfere with the subject's ability to communicate with the magnet operator. Additionally, some people might feel claustrophobic in the magnet, and if this is the case the study can be ended early.

While all information about the subject's participation in this research will be handled in a confidential manner, a breach of confidentiality is another potential risk present in this study. All data collected during the procedures of this study will be labeled only with an assigned research code number; and only certified members of the research team will have access to the identity of any participant.

Although there are no known risks for pregnant women to go through a MRI procedure, we will exclude women who are pregnant for this study.

Although the MRI scans are conducted to answer research questions; there is a possibility that we may detect something unusual or different within your results. In this unlikely event, the neurosurgeon or neuropsychologist will discuss these findings with you. The results of the research MRI will not become part of the subject's hospital record.

Benefits of Participation:

There is no direct benefit for participating in this study. This study will provide a better understanding the neural signatures of stuttering eventually leading to individualized treatment plans.

Compensation for participating in the study:

None of the procedures described in this protocol are performed as a part of standard clinical care, and no third party providers (insurance companies) will be charged for any of these procedures. Participants will be paid $25.00 for completing research study.

Compensation for injury as a result of taking part in the study:

University of Pittsburgh researchers and associates will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please immediately contact the principal investigator listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Data acquisition and management:

All identifiable records and data will be kept confidential, in locked files and password protected computer files. These files are only accessible to researchers involved in the study. The records will be de-identified by using a case number. The de-identified records will be maintained in a separate location for a minimum of seven years.

Disclosure of identifiable medical information:

Medical information will not be used in this research study. The information obtained as part of the study (MRI scans) will be used for understanding the neurological basis of stuttering. All information acquired as part of the study will be maintained with utmost confidentiality. The information will not be accessible to third party, including relatives, insurance companies or other researchers except with a few exceptions mentioned in the following section.

Access to identifiable information:

Investigators listed on the first page of this consent form will have access to your identifiable information. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable information for the purpose of monitoring the appropriate conduct of this research study.

Voluntary participation:

Participation in this study is completely voluntary and you have the right to withdraw from participation at any time and for any reason. If you do decide to withdraw, all data acquired up until that point in the study would be retained for use in our analysis.

Questions about the study:

If you have any questions about the study please contact the principal investigators listed on the first page of this form. Questions about your rights as a research participant can be directed to Human Subjects Protection Advocate at the University of Pittsburgh IRB Office, 1-866-212-2668.

VOLUNTARY CONSENT

• I have read the consent form for this study and any questions I had, including explanation of all terminology, have been answered to my satisfaction. A copy of this consent form will be provided to me.

• I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that those questions will be answered by the researchers listed on the first page of this form.

• I understand that my participation in this study is voluntary and that I am free to refuse to participate or to withdraw my consent and discontinue my participation in this study at any time without affecting my future relationship with this institution.

• I agree to participate in this study.

_____ _____
_____

Date & Time Subject's Signature Subject's Printed Name

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date/Time

APPENDIX B

MEAN AND STANDARD DEVIATIONS OF TRACTS

Table 22: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere RO to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0881406	0.0345671	0.101856	0.0540367	5496.64
2	Stuttering	0.099084	0.0315642	0.116218	0.0547869	11489.2
3	Stuttering	0.0939401	0.0313663	0.115972	0.0567144	2038.85
4	Stuttering	0.0999114	0.0335643	0.134585	0.0619216	12026.5
5	Stuttering	0.100215	0.036252	0.0715744	0.0331853	4559.87
6	Stuttering	0.102528	0.0374838	0.0998912	0.044014	5455.31
7	Stuttering	0.0993065	0.0311407	0.108929	0.0435551	15718.5
8	Control	0.0925408	0.0405019	0.163008	0.100498	9229.95
9	Control	0.103704	0.0307613	0.103704	0.0450045	13569.4
10	Control	0.112945	0.0359006	0.118233	0.0472426	9780.99
11	Control	0.101018	0.033283	0.104392	0.0478589	9326.38
12	Control	0.107733	0.0331787	0.136593	0.0548042	8045.21
13	Control	0.108436	0.0389862	0.099794	0.0596609	8486.04
14	Control	0.108976	0.0306509	0.0660302	0.0239573	20912

Table 23: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere Spt to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0886137	0.0351238	0.0902606	0.0345825	1405.16
2	Stuttering	0.105805	0.0296202	0.0937477	0.0339299	1611.8
3	Stuttering	0.0983067	0.0276113	0.0899152	0.0236105	303.073
4	Stuttering	0.0828099	0.0303189	0.0899496	0.0330122	303.073
5	Stuttering	0.103941	0.033659	0.0699674	0.0247824	2548.57
6	Stuttering	0.0727516	0.025723	0.061097	0.0208255	1212.29
7	Stuttering	0.0859846	0.024853	0.0751464	0.0199829	3691.98
8	Control	0.0985674	0.0232733	0.126736	0.0422521	2231.72
9	Control	0.102519	0.0282046	0.0865431	0.0279197	5000.7
10	Control	0.0807573	0.0275569	0.0773088	0.0200971	1033.2
11	Control	0.0862495	0.0369669	0.0806618	0.0329069	2259.27
12	Control	0.0940152	0.0250555	0.0853412	0.0279463	4807.84
13	Control	0.124691	0.0321572	0.08156	0.0273473	12412.2
14	Control	0.0972101	0.0315344	0.0540278	0.0186995	6722.71

Table 24: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere Spt to HG

Participants	Group	FA	FA SD	QA	Tract volume (mm^3)
1	Stuttering	0	0	0	0
2	Stuttering	0	0	0	0
3	Stuttering	0	0	0	0
4	Stuttering	0	0	0	0
5	Stuttering	0	0	0	0
6	Stuttering	0	0	0	0
7	Stuttering	0.0747531	0.0233212	0.0659938	619.922
8	Control	0	0	0	0
9	Control	0	0	0	0
10	Control	0	0	0	0
11	Control	0	0	0	0
12	Control	0.0872759	0.0207728	0.0761883	289.297
13	Control	0.0910467	0.0910467	0.0580482	509.714
14	Control	0	0	0	0

Table 25: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere HG to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0980182	0.0403352	0.112805	0.0687241	10690.2
2	Stuttering	0.119807	0.041659	0.126088	0.0611081	1845.99
3	Stuttering	0	0	0	0	0
4	Stuttering	0.112826	0.0376891	0.130596	0.0545673	509.713
5	Stuttering	0	0	0	0	0
6	Stuttering	0.113332	0.0364229	0.117208	0.0551045	4077.71
7	Stuttering	0.120096	0.0383172	0.123621	0.0446281	9037.08
8	Control	0.0923856	0.028718	0.144969	0.0637986	3774.64
9	Control	0.114309	0.0359615	0.120888	0.0453888	1253.62
10	Control	0.115581	0.0434276	0.130613	0.0706094	3912.4
11	Control	0.104019	0.0371084	0.112013	0.0481165	5193.57
12	Control	0.102539	0.0341943	0.132263	0.0637474	4105.26
13	Control	0.111166	0.0301953	0.0926246	0.0356376	1046.98
14	Control	0.102939	0.0356196	0.0599752	0.0273038	1598.02

Table 26: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere Spt to SMG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0822961	0.0298714	0.0887627	0.0307062	2121.51
2	Stuttering	0.0926398	0.0287057	0.0788004	0.0233473	5675.73
3	Stuttering	0.0933458	0.0216558	0.090754	0.0180648	2259.27
4	Stuttering	0.0902142	0.0253815	0.100197	0.0299223	1198.52
5	Stuttering	0.0894655	0.0348961	0.0629398	0.0280528	4862.94
6	Stuttering	0.0770515	0.0240833	0.0702575	0.0248276	3981.28
7	Stuttering	0.0705362	0.0293	0.0718583	0.0260275	7411.51
8	Control	0.0883338	0.0262111	0.113861	0.0377712	6970.68
9	Control	0.0822383	0.0271405	0.0802138	0.029056	9546.8
10	Control	0.0689535	0.0278896	0.0731761	0.0271109	6061.46
11	Control	0.0693337	0.0278556	0.0743264	0.0282377	5785.94
12	Control	0.0948246	0.0319322	0.0899742	0.029132	5854.82
13	Control	0.0943333	0.0410672	0.0581313	0.0278257	7315.08
14	Control	0.0873268	0.0259174	0.0416877	0.0138769	10855.5

Table 27: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere Spt to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0977678	0.0392036	0.114255	0.0488894	1777.11
2	Stuttering	0.125694	0.0368273	0.127972	0.0522694	1735.78
3	Stuttering	0	0	0	0	0
4	Stuttering	0.116465	0.0319614	0.143087	0.0488738	1790.89
5	Stuttering	0	0	0	0	0
6	Stuttering	0.123765	0.0251397	0.133521	0.0336974	2286.82
7	Stuttering	0.119383	0.0407838	0.127832	0.0472346	5537.97
8	Control	0	0	0	0	0
9	Control	0.114178	0.0362929	0.124812	0.0424257	1267.4
10	Control	0.104371	0.0457964	0.117042	0.0548936	3127.16
11	Control	0.102704	0.0388436	0.116099	0.0566881	4146.59
12	Control	0.113982	0.0419747	0.140353	0.0586206	6295.65
13	Control	0.13177	0.0461551	0.0993727	0.0404167	509.714
14	Control	0.116563	0.0398959	0.0752022	0.0313803	6075.23

Table 28: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere IFG to Spt

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0.129466	0.0324973	0.131354	0.0417778	8692.68
4	Stuttering	0.120611	0.0293346	0.143862	0.0415781	716.354
5	Stuttering	0.117944	0.0378656	0.0758335	0.0241268	10097.8
6	Stuttering	0.121819	0.0248316	0.111204	0.0336739	4670.08
7	Stuttering	0	0	0	0	0
8	Control	0.126004	0.0365806	0.201132	0.0704743	9477.92
9	Control	0.125435	0.0280677	0.103152	0.0355507	2066.41
10	Control	0.11113	0.0216224	0.0961064	0.0256502	1198.52
11	Control	0.110328	0.0325948	0.105009	0.0356581	3912.4
12	Control	0.116755	0.0338243	0.121333	0.0416559	3292.47
13	Control	0.104868	0.0319192	0.0719759	0.023037	3016.95
14	Control	0	0	0	0	0

Table 29: Mean and Standard deviations (SD) of Fractional Anisotropy (FA), Quantitative anisotropy (QA) and Tract volume for left hemisphere SMG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.091075	0.0280246	0.0888317	0.0289384	6970.68
2	Stuttering	0.103107	0.0291419	0.0915759	0.0297839	9312.6
3	Stuttering	0.105667	0.0320376	0.100051	0.0352182	2906.74
4	Stuttering	0.0960787	0.0260814	0.100055	0.0287842	6998.23
5	Stuttering	0.085356	0.0301875	0.0519847	0.0172498	5772.16
6	Stuttering	0.0782029	0.0280267	0.0607944	0.0219373	5317.55
7	Stuttering	0.0880264	0.0254943	0.0756288	0.0199748	4490.99
8	Control	0.0887987	0.0300789	0.118536	0.0470741	2204.17
9	Control	0.101345	0.0239444	0.0840383	0.0214767	6350.75
10	Control	0.0721567	0.0241706	0.0626257	0.0192894	3981.28
11	Control	0.0793413	0.0373634	0.0702775	0.0309889	6433.41
12	Control	0.0933744	0.027426	0.0849785	0.0274236	6447.19
13	Control	0.101372	0.0223645	0.0637049	0.0177544	4780.29
14	Control	0.11243	0.0279751	0.0608972	0.019019	9009.53

Table 30: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere SMG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.091075	0.0280246	0.0888317	0.0289384	6970.68
2	Stuttering	0.103107	0.0291419	0.0915759	0.0297839	9312.6
3	Stuttering	0.105667	0.0320376	0.100051	0.0352182	2906.74
4	Stuttering	0.0960787	0.0260814	0.100055	0.0287842	6998.23
5	Stuttering	0.085356	0.0301875	0.0519847	0.0172498	5772.16
6	Stuttering	0.0782029	0.0280267	0.0607944	0.0219373	5317.55
7	Stuttering	0.0880264	0.0254943	0.0756288	0.0199748	4490.99
8	Control	0.0887987	0.0300789	0.118536	0.0470741	2204.17
9	Control	0.101345	0.0239444	0.0840383	0.0214767	6350.75
10	Control	0.0721567	0.0241706	0.0626257	0.0192894	3981.28
11	Control	0.0793413	0.0373634	0.0702775	0.0309889	6433.41
12	Control	0.0933744	0.027426	0.0849785	0.0274236	6447.19
13	Control	0.101372	0.0223645	0.0637049	0.0177544	4780.29
14	Control	0.11243	0.0279751	0.0608972	0.019019	9009.53

Table 31: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere SMG to HG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0.0971255	0.0329296	0.0782547	0.0251089	2107.73
3	Stuttering	0	0	0	0	0
4	Stuttering	0.0728903	0.0258309	0.073511	0.0249641	2080.18
5	Stuttering	0.0660293	0.0243441	0.0408631	0.0133195	468.385
6	Stuttering	0.0616096	0.0162178	0.048078	0.0126111	922.995
7	Stuttering	0.0633273	0.0197725	0.0562558	0.0155054	1198.52
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0.0725978	0.022019	0.0632136	0.0170397	1598.02
11	Control	0	0	0	0	0
12	Control	0.0728563	0.027916	0.0688334	0.021528	1790.89
13	Control	0.0787032	0.0167727	0.0467879	0.0110155	1074.53
14	Control	0.0799598	0.0182028	0.0381021	0.0068729	1129.64

Table 32: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere HG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0708256	0.0232746	0.0564328	0.018367	5303.78
2	Stuttering	0.0928811	0.029521	0.0730826	0.0303291	261.745
3	Stuttering	0.0777244	0.0274656	0.0690553	0.0257371	619.922
4	Stuttering	0.054952	0.010127	0.056277	0.0119042	468.385
5	Stuttering	0.0612013	0.0134351	0.0345163	0.00835316	3829.74
6	Stuttering	0.0732693	0.0228366	0.0574565	0.0187689	2093.96
7	Stuttering	0.0983636	0.0253792	0.0817179	0.0221547	909.219
8	Control	0.0678467	0.0169785	0.0823073	0.0224384	289.297
9	Control	0	0	0	0	0
10	Control	0.0761159	0.0256325	0.0629807	0.0222672	1639.35
11	Control	0.0660559	0.0288633	0.0572019	0.0283015	2410.81
12	Control	0.0630928	0.0254322	0.0623042	0.0281181	1501.59
13	Control	0.0767416	0.0285233	0.0466186	0.0222659	2576.12
14	Control	0.0690253	0.0118001	0.0343978	0.0058002	909.219

Table 33: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere IFG to SMG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.103497	0.0358621	0.102639	0.045085	4215.47
2	Stuttering	0.110299	0.0387637	0.0888402	0.0386477	1033.2
3	Stuttering	0.128341	0.0348998	0.131309	0.0457081	10125.4
4	Stuttering	0.121968	0.0299173	0.14543	0.0413902	950.547
5	Stuttering	0	0	0	0	0
6	Stuttering	0.108916	0.0233203	0.0875164	0.0223174	6777.81
7	Stuttering	0	0	0	0	0
8	Control	0.103089	0.0241452	0.133579	0.0452604	1928.65
9	Control	0.103183	0.0204791	0.0923138	0.0235344	1170.96
10	Control	0	0	0	0	0
11	Control	0.108977	0.0344698	0.10327	0.0357606	978.099
12	Control	0.11359	0.0351171	0.120295	0.0395396	454.609
13	Control	0.103603	0.03211	0.0710563	0.0233143	2273.05
14	Control	0	0	0	0	0

Table 34: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere IFG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0887805	0.0346397	0.0893506	0.032946	3719.53
2	Stuttering	0.078795	0.0174179	0.0890811	0.023749	440.833
3	Stuttering	0.0955003	0.0271425	0.101662	0.0269788	2176.61
4	Stuttering	0.104861	0.0360332	0.111203	0.0401521	647.474
5	Stuttering	0.071548	0.0292345	0.0451425	0.0166974	1322.5
6	Stuttering	0.125266	0.0274084	0.109413	0.032512	4050.16
7	Stuttering	0.0580588	0.0242667	0.0605017	0.0198686	909.219
8	Control	0.0915646	0.0241359	0.123494	0.038709	2162.84
9	Control	0.0951062	0.024955	0.0863074	0.0210596	2025.08
10	Control	0.0788737	0.0232614	0.0687146	0.0203984	1680.68
11	Control	0.0825981	0.0304809	0.0721826	0.0218379	1281.17
12	Control	0.0872458	0.0321608	0.0917164	0.0302667	1226.07
13	Control	0.0738581	0.0307453	0.0538277	0.0194323	3306.25
14	Control	0.0798839	0.0306991	0.0384851	0.0155313	3196.04

Table 35: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere IFG to HG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0726521	0.0247463	0.0692893	0.0250178	785.234
2	Stuttering	0	0	0	0	0
3	Stuttering	0.0929921	0.0251293	0.104429	0.0424523	922.995
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 36: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere IFG to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0862759	0.0323526	0.105292	0.0492556	21573.3
2	Stuttering	0.101577	0.0353439	0.125106	0.0473905	17371.6
3	Stuttering	0.0915307	0.0285196	0.11501	0.0432769	20595.2
4	Stuttering	0.0976418	0.0366909	0.140208	0.0652812	19438
5	Stuttering	0.0845525	0.0285409	0.0567942	0.0234462	12246.9
6	Stuttering	0.102042	0.0304489	0.0888633	0.0319273	14519.9
7	Stuttering	0.0903525	0.0325799	0.0963984	0.0420534	16999.6
8	Control	0.0905052	0.0291021	0.131668	0.0418749	8513.59
9	Control	0.0961482	0.0338512	0.110387	0.0463731	23088.6
10	Control	0.0951351	0.0317707	0.0906069	0.0445064	20402.3
11	Control	0.0837184	0.0330758	0.0816647	0.0389918	15718.5
12	Control	0.092456	0.034601	0.116316	0.0472948	33007.4
13	Control	0.0876229	0.0375824	0.0768047	0.0372264	24714.2
14	Control	0.0996543	0.0309608	0.0602375	0.0230083	29770

Table 37: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Left hemisphere SMG to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.106504	0.0375321	0.121207	0.0564656	5841.04
2	Stuttering	0.116696	0.0394918	0.140386	0.060037	1969.97
3	Stuttering	0	0	0	0	0
4	Stuttering	0.124651	0.0329708	0.151184	0.0562393	371.953
5	Stuttering	0	0	0	0	0
6	Stuttering	0.110824	0.0301164	0.114724	0.0314143	4725.18
7	Stuttering	0.115991	0.0412178	0.128313	0.0504797	6722.71
8	Control	0	0	0	0	0
9	Control	0.113851	0.0263761	0.103164	0.0371554	385.729
10	Control	0	0	0	0	0
11	Control	0.111994	0.0326974	0.113746	0.0344372	895.443
12	Control	0.107263	0.0376863	0.131615	0.0547141	7149.76
13	Control	0.107758	0.0350013	0.0945807	0.0425377	2672.55
14	Control	0	0	0	0	0

Table 38: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere RO to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.100281	0.0334498	0.117815	0.0491579	12797.9
2	Stuttering	0.0878661	0.0413072	0.103122	0.0535062	18156.8
3	Stuttering	0.0847732	0.0339777	0.101222	0.0488859	5689.5
4	Stuttering	0.105877	0.0391885	0.152894	0.0753197	11337.7
5	Stuttering	0.0974552	0.0335669	0.0621483	0.0276958	19134.9
6	Stuttering	0.0970481	0.0265133	0.0934975	0.0301175	7700.81
7	Stuttering	0.0742175	0.03356	0.0754515	0.0368073	7397.73
8	Control	0.108121	0.0399153	0.108726	0.0541331	17771.1
9	Control	0.115736	0.0339838	0.140554	0.0578988	11310.1
10	Control	0.0788575	0.0244312	0.112543	0.0382079	5138.46
11	Control	0.0813538	0.0397371	0.0877634	0.0473766	19575.8
12	Control	0.1067	0.0359256	0.131786	0.0658695	12605.1
13	Control	0.0878853	0.034791	0.0684841	0.0342773	12219.3
14	Control	0.0979685	0.0322937	0.0659939	0.022922	30596.6

Table 39: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere HG to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0609532	0.019192	0.0487958	0.0133541	3609.32
2	Stuttering	0.109651	0.0400877	0.113634	0.0510098	2066.41
3	Stuttering	0.101425	0.0249736	0.122354	0.0475995	1446.48
4	Stuttering	0	0	0	0	0
5	Stuttering	0.101936	0.0340307	0.069968	0.0311819	5551.74
6	Stuttering	0	0	0	0	0
7	Stuttering	0.10692	0.0364168	0.101924	0.0450672	6171.67
8	Control	0.112518	0.0395086	0.11413	0.0592107	7618.15
9	Control	0.111314	0.0336029	0.126834	0.0534015	1694.45
10	Control	0.0930655	0.0272603	0.131232	0.0548895	4890.49
11	Control	0.104582	0.0342084	0.114154	0.0428082	5193.57
12	Control	0.0954971	0.0298108	0.11136	0.0494692	8665.13
13	Control	0.107551	0.0345066	0.0886892	0.045975	3926.17
14	Control	0.0999079	0.0309751	0.060316	0.0210627	7604.37

Table 40: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere SMG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0685856	0.0250141	0.0586466	0.0197552	12012.7
2	Stuttering	0.0891963	0.0247701	0.072802	0.0275539	12467.3
3	Stuttering	0.0914376	0.0263269	0.0864756	0.0249267	4931.82
4	Stuttering	0.0787255	0.0274243	0.0853404	0.0334662	7191.09
5	Stuttering	0.078104	0.025016	0.0457443	0.0136892	5813.49
6	Stuttering	0.08278	0.0218204	0.0570972	0.0156594	5083.36
7	Stuttering	0.0878586	0.0243323	0.0750295	0.0204801	6819.14
8	Control	0.0835548	0.0280789	0.0709017	0.020104	7769.69
9	Control	0.0977419	0.0229318	0.0840577	0.0214895	6777.81
10	Control	0.073986	0.0216661	0.0965719	0.031014	5276.22
11	Control	0.067984	0.0249377	0.0721475	0.0196307	9863.65
12	Control	0.0764381	0.0357621	0.0877467	0.0423679	6047.68
13	Control	0.0953546	0.0266664	0.0566722	0.0169082	7204.87
14	Control	0.070358	0.0248593	0.0398884	0.010844	14079.1

Table 41: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere SMG to HG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0700142	0.0256037	0.0580558	0.0193991	2493.46
2	Stuttering	0.0804424	0.0223546	0.0627811	0.0198343	3733.31
3	Stuttering	0.0993897	0.0323506	0.0972545	0.0308405	854.115
4	Stuttering	0	0	0	0	0
5	Stuttering	0.0723865	0.0218217	0.0421553	0.0112656	344.401
6	Stuttering	0.0949919	0.0192783	0.0694405	0.0152432	2438.36
7	Stuttering	0.0935036	0.0248044	0.0800368	0.0209483	743.906
8	Control	0.0818178	0.0259211	0.0707741	0.0196593	2038.85
9	Control	0	0	0	0	0
10	Control	0.0926661	0.0218105	0.101287	0.0276221	564.818
11	Control	0.0600782	0.0211003	0.0590348	0.0156565	2052.63
12	Control	0.0874389	0.0288805	0.0849971	0.0255668	840.338
13	Control	0.0852643	0.0268897	0.0509388	0.0155879	3044.51
14	Control	0.0592503	0.0253358	0.0375898	0.0097929	468.385

Table 42: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere HG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.072287	0.0215486	0.0599888	0.0181875	2768.98
2	Stuttering	0.06957	0.0188724	0.0569359	0.0204534	1405.16
3	Stuttering	0	0	0	0	0
4	Stuttering	0.0734557	0.0219486	0.0690872	0.016821	1887.32
5	Stuttering	0.0510388	0.0179913	0.0303448	0.00967418	3251.15
6	Stuttering	0.0717534	0.0225939	0.0613119	0.0124189	440.833
7	Stuttering	0.0606221	0.0179004	0.0484186	0.0123662	950.547
8	Control	0.073152	0.0163564	0.0552799	0.012959	1350.05
9	Control	0.0637565	0.0164049	0.0550348	0.0132623	1446.48
10	Control	0.0696092	0.0151441	0.0822691	0.0224439	1515.36
11	Control	0.0564753	0.0219411	0.0504017	0.0153595	6612.5
12	Control	0.0553421	0.0182464	0.0554623	0.0160791	2424.58
13	Control	0.0782868	0.016957	0.0474495	0.0140242	427.057
14	Control	0.0605197	0.0184659	0.0371136	0.0097274	3361.35

Table 43: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere IFG to SMG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.105264	0.0370346	0.110701	0.0393088	5248.67
2	Stuttering	0.130243	0.0401688	0.139533	0.04864	4394.56
3	Stuttering	0.11611	0.0322276	0.136451	0.0384379	8665.13
4	Stuttering	0.113389	0.0409112	0.141238	0.0505705	7521.72
5	Stuttering	0.0955823	0.0308646	0.0590187	0.0204896	11268.8
6	Stuttering	0.123934	0.0354073	0.108358	0.0332182	7907.45
7	Stuttering	0.114238	0.0326621	0.10932	0.0370504	7232.42
8	Control	0.107766	0.0267231	0.100533	0.0238974	2397.03
9	Control	0.120278	0.0268593	0.117229	0.0273154	936.771
10	Control	0.105643	0.027636	0.140725	0.0431061	1942.42
11	Control	0.105117	0.0345852	0.100149	0.0398058	16062.9
12	Control	0.100672	0.0338471	0.0948393	0.0361325	5469.09
13	Control	0.118178	0.0351712	0.081068	0.0248507	7687.03
14	Control	0.0969697	0.0307986	0.0587921	0.0212038	3140.94

Table 44: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere IFG to RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0865271	0.0378589	0.0933656	0.040875	2521.02
2	Stuttering	0.0798428	0.0395316	0.0862631	0.0425717	9161.07
3	Stuttering	0.0715542	0.0299871	0.0766843	0.0279373	1363.83
4	Stuttering	0.0656299	0.0285557	0.0858565	0.0309812	3237.37
5	Stuttering	0.0559247	0.022057	0.0350362	0.013215	10139.2
6	Stuttering	0.0941697	0.0307026	0.0777046	0.0222939	3471.56
7	Stuttering	0.0658792	0.0213912	0.0629279	0.0180618	2727.66
8	Control	0.0838325	0.0312703	0.0791457	0.0237583	1184.74
9	Control	0.09522	0.0354279	0.103975	0.0413813	4008.83
10	Control	0.0917577	0.0238447	0.140994	0.0480037	5124.69
11	Control	0.0619345	0.0202901	0.0608364	0.0208184	5455.31
12	Control	0.0973701	0.0370975	0.112517	0.0434871	5551.74
13	Control	0.0802932	0.0346293	0.0576367	0.0224369	5097.14
14	Control	0.0898144	0.0317562	0.0539665	0.0179022	2245.49

Table 45: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere IFG to HG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0	0	0	0	0
5	Stuttering	0.0655658	0.0193782	0.0404303	0.0114486	509.714
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0.0500401	0.0127546	0.0421907	0.00440581	137.76
10	Control	0	0	0	0	0
11	Control	0.0633683	0.0276692	0.054272	0.0221191	1363.83
12	Control	0.079315	0.0244219	0.071223	0.0179618	1474.04
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 46: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere IFG to PM

Participant	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0967653	0.0427721	0.10913	0.0571896	32235.9
2	Stuttering	0.0724755	0.040633	0.0848709	0.0478659	20099.2
3	Stuttering	0.0959166	0.0336457	0.126222	0.0540683	25320.4
4	Stuttering	0.0839262	0.0337096	0.116442	0.0497268	17964
5	Stuttering	0.0757329	0.0335669	0.0527298	0.0259103	31795.1
6	Stuttering	0.0972319	0.0306559	0.0861674	0.0286209	14120.4
7	Stuttering	0.114117	0.039147	0.113197	0.0510884	12026.5
8	Control	0.0967481	0.034188	0.0911451	0.0339919	14919.5
9	Control	0.101429	0.0335522	0.120126	0.0498019	19272.7
10	Control	0.0938357	0.0332673	0.148165	0.0595475	13858.7
11	Control	0.0980008	0.0395181	0.0975453	0.0535639	29590.9
12	Control	0.0834308	0.0332324	0.0996525	0.0481936	21779.9
13	Control	0.08874	0.0376965	0.0727562	0.0431913	27028.6
14	Control	0.0937928	0.0309919	0.0617457	0.0232307	19920.2

Table 47: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere Spt to RO

Participants		FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0532308	0.0173123	0.0435122	0.0116072	4187.92
2	Stuttering	0.0894337	0.0343108	0.0757149	0.0399096	6819.14
3	Stuttering	0.0806703	0.0263357	0.0757087	0.0241798	3223.59
4	Stuttering	0.0890408	0.0332448	0.101479	0.0406449	5358.88
5	Stuttering	0.0945192	0.0300614	0.0523094	0.0150813	3044.51
6	Stuttering	0.102276	0.0264533	0.0897753	0.0287975	2369.48
7	Stuttering	0.0574716	0.023706	0.0509897	0.0203898	1556.69
8	Control	0.0638434	0.0210217	0.0600712	0.0175948	3375.13
9	Control	0.078977	0.0226821	0.0677358	0.0179369	3691.98
10	Control	0.0668262	0.0156759	0.0859646	0.020295	5882.37
11	Control	0.0632496	0.0255054	0.0608069	0.0210692	7755.91
12	Control	0.0636452	0.0215984	0.068528	0.0208227	1005.65
13	Control	0.0799593	0.0242618	0.0499991	0.0166705	6626.28
14	Control	0.0685004	0.0270926	0.0389145	0.0107875	11434.1

Table 48: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere Spt to HG

Participant	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0644365	0.0233847	0.0518166	0.0154203	1239.84
2	Stuttering	0.0857151	0.0181844	0.0652708	0.0187107	1198.52
3	Stuttering	0.101041	0.0297488	0.094814	0.0285947	702.578
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0.0838712	0.0291399	0.0689258	0.0226867	3416.46
9	Control	0.0784961	0.0209865	0.0688527	0.0142358	482.161
10	Control	0.0927756	0.0216715	0.101095	0.0277016	564.818
11	Control	0.0559625	0.019062	0.0536479	0.0145591	3747.08
12	Control	0.0882391	0.0284563	0.0854758	0.0251591	881.667
13	Control	0.0838816	0.0211125	0.0465516	0.0136806	2286.82
14	Control	0.0596702	0.0228208	0.0378126	0.00893913	1336.28

Table 49: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere Spt to SMG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0654922	0.029291	0.0607577	0.0224131	7383.96
2	Stuttering	0.0667402	0.0288741	0.05449	0.0162208	5276.22
3	Stuttering	0.0663942	0.0205085	0.0693452	0.0149693	4256.8
4	Stuttering	0.0745331	0.0301485	0.0820548	0.0315123	7948.77
5	Stuttering	0.0622755	0.0179635	0.0385854	0.00840984	2824.09
6	Stuttering	0.0898269	0.0221155	0.0664098	0.0167419	3678.2
7	Stuttering	0.067352	0.0271701	0.0628541	0.0184883	6846.69
8	Control	0	0	0	0	0
9	Control	0.0953213	0.0259351	0.0851432	0.02384	4119.04
10	Control	0.0763265	0.0232957	0.0951907	0.0300253	8830.44
11	Control	0.0712156	0.0321047	0.075721	0.0313435	7425.29
12	Control	0	0	0	0	0
13	Control	0.0844714	0.0258564	0.0464523	0.0128329	6736.48
14	Control	0.0687082	0.025538	0.035518	0.0105702	12329.6

Table 50: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere Spt to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.0936969	0.0387251	0.0975778	0.0535206	3388.91
2	Stuttering	0	0	0	0	0
3	Stuttering	0.105894	0.0319391	0.125085	0.0452563	2507.24
4	Stuttering	0	0	0	0	0
5	Stuttering	0.100658	0.0393008	0.0658948	0.040318	1294.95
6	Stuttering	0.108027	0.0267174	0.0969353	0.0309948	1432.71
7	Stuttering	0.118326	0.0361484	0.110758	0.0381532	2837.86
8	Control	0.116444	0.0404206	0.11888	0.0639624	11131
9	Control	0	0	0	0	0
10	Control	0.103312	0.0323454	0.156229	0.0704011	10015.2
11	Control	0.0986137	0.0378849	0.10002	0.0500885	13087.2
12	Control	0.112069	0.0386069	0.138903	0.0738621	1584.24
13	Control	0.0954321	0.0337942	0.0681017	0.0308336	936.771
14	Control	0.101849	0.029692	0.0611968	0.0221077	10993.3

Table 51: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere IFG to Spt

Participant	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.097905	0.0340019	0.101002	0.0365668	4050.16
2	Stuttering	0.10218	0.033031	0.0864994	0.0284239	1832.21
3	Stuttering	0.114029	0.0327874	0.125991	0.0384325	1983.75
4	Stuttering	0.0984928	0.0231894	0.105034	0.0271777	1722.01
5	Stuttering	0.0881729	0.0284679	0.0507435	0.0167275	1969.97
6	Stuttering	0.125778	0.035252	0.112557	0.0330605	8417.16
7	Stuttering	0.0846769	0.0252616	0.0658522	0.0167354	2355.7
8	Control	0.10089	0.0263382	0.089447	0.0216754	3926.17
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0.10343	0.0252672	0.0925512	0.0284797	2025.08
12	Control	0.0906922	0.0232689	0.09013	0.0221431	2052.63
13	Control	0.111228	0.0309264	0.0689382	0.0224253	2204.17
14	Control	0.101784	0.0339476	0.0661199	0.0235547	2176.61

Table 52: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of Right hemisphere SMG to PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.132729	0.0465501	0.113127		3237.37
2	Stuttering	0.0757528	0.0346651	0.0701984	0.0380933	3457.79
3	Stuttering	0	0	0	0	0
4	Stuttering	0.123757	0.0361284	0.0860139	0.0484	1253.62
5	Stuttering	0.073323	0.0359661	0.112418	0.0287959	11048.4
6	Stuttering	0.110714	0.0370385	0.11986	0.0426888	1694.45
7	Stuttering	0.123401	0.0336229	0.118836	0.0388828	7025.78
8	Control	0.0940747	0.0312808	0.100272	0.0360968	1763.33
9	Control	0	0	0	0	0
10	Control	0.112243	0.0387429	0.0831438	0.0477782	592.37
11	Control	0.127898	0.0363822	0.114385	0.0480426	3636.87
12	Control	0.153018	0.0289354	0.11764	0.0504937	2300.6
13	Control	0	0	0	0	0
14	Control	0.084801	0.0364422	0.118677	0.0327451	3829.74

Table 53: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections SMG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0.135213	0.0499901	0.117929	0.0567991	1281.17
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 54: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections IFG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0.102844	0.0359517	0.118943	0.0474346	5510.42
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 55: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections RO

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0.111538	0.0327117	0.123274	0.0554625	1157.19
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 56: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections HG

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

Table 57: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections PM

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0.108572	0.036397	0.135003	0.0572986	18170.6
2	Stuttering	0.123899	0.042885	0.168461	0.0694493	14106.7
3	Stuttering	0.115052	0.0423914	0.168382	0.0715442	21215.1
4	Stuttering	0.123436	0.0455533	0.185237	0.102343	4243.02
5	Stuttering	0.111873	0.0351236	0.0913398	0.0374807	3967.5
6	Stuttering	0.117761	0.035365	0.145775	0.0484599	950.547
7	Stuttering	0.102707	0.0316444	0.11455	0.0407163	3016.95
8	Control	0.0933852	0.0273815	0.179863	0.0604546	3499.11
9	Control	0.109914	0.036287	0.124598	0.0537411	15828.7
10	Control	0.127659	0.0433181	0.128859	0.0560564	1570.47
11	Control	0.11172	0.0367873	0.12358	0.051558	8527.37
12	Control	0.111162	0.0352538	0.150428	0.0566821	1267.4
13	Control	0.124124	0.0457299	0.119527	0.0501559	7397.73
14	Control	0.128211	0.033385	0.0921401	0.0323495	4160.36

Table 58: Mean and standard deviation (SD) of Fractional Anisotropy (FA), Quantitative Anisotropy (QA) and Tract Volume of interhemisphere connections Spt

Participants	Group	FA	FA SD	QA	QA SD	Tract volume (mm^3)
1	Stuttering	0	0	0	0	0
2	Stuttering	0	0	0	0	0
3	Stuttering	0	0	0	0	0
4	Stuttering	0	0	0	0	0
5	Stuttering	0	0	0	0	0
6	Stuttering	0	0	0	0	0
7	Stuttering	0	0	0	0	0
8	Control	0	0	0	0	0
9	Control	0	0	0	0	0
10	Control	0	0	0	0	0
11	Control	0	0	0	0	0
12	Control	0	0	0	0	0
13	Control	0	0	0	0	0
14	Control	0	0	0	0	0

APPENDIX C

TRACT VOLUME COMPARISONS BETWEEN PEOPLE WHO STUTTER AND PEOPLE WHO DO NTO STUTTER

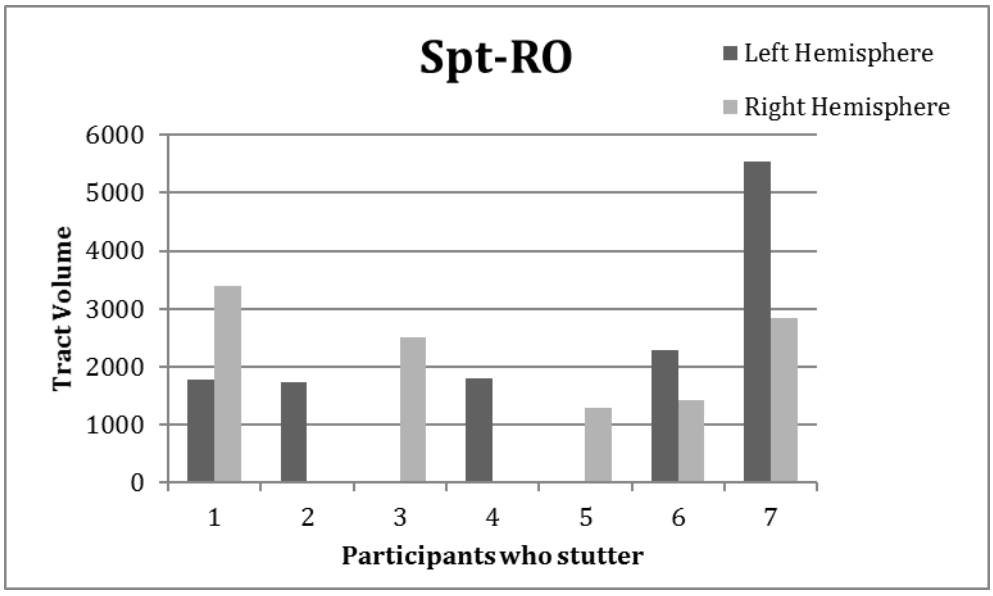


Figure 21: Tract volumes in left and right hemispheres of Spt-RO in participants who stutter

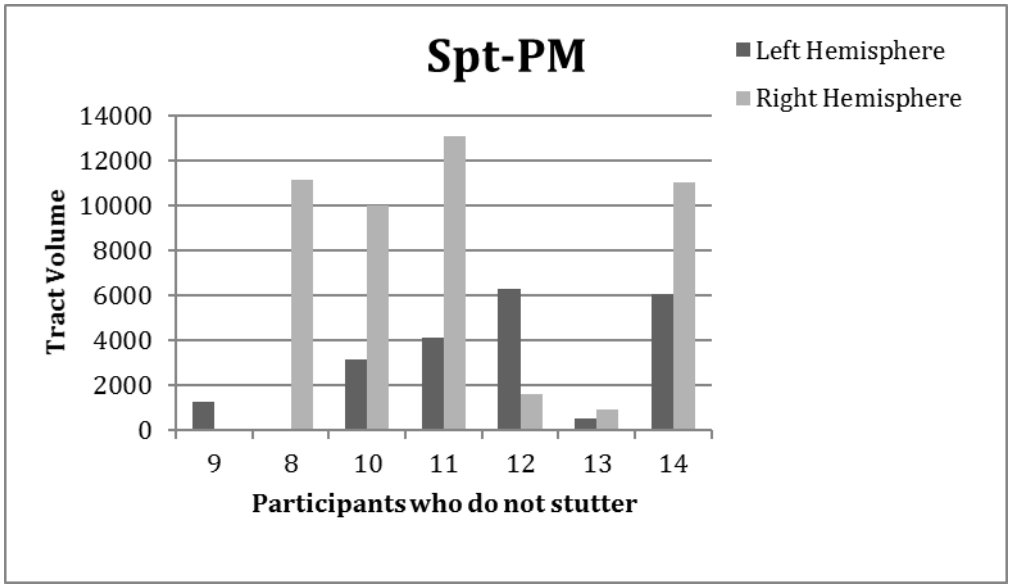


Figure 22: Tract volumes in left and right hemispheres of Spt-RO in participants who do not stutter

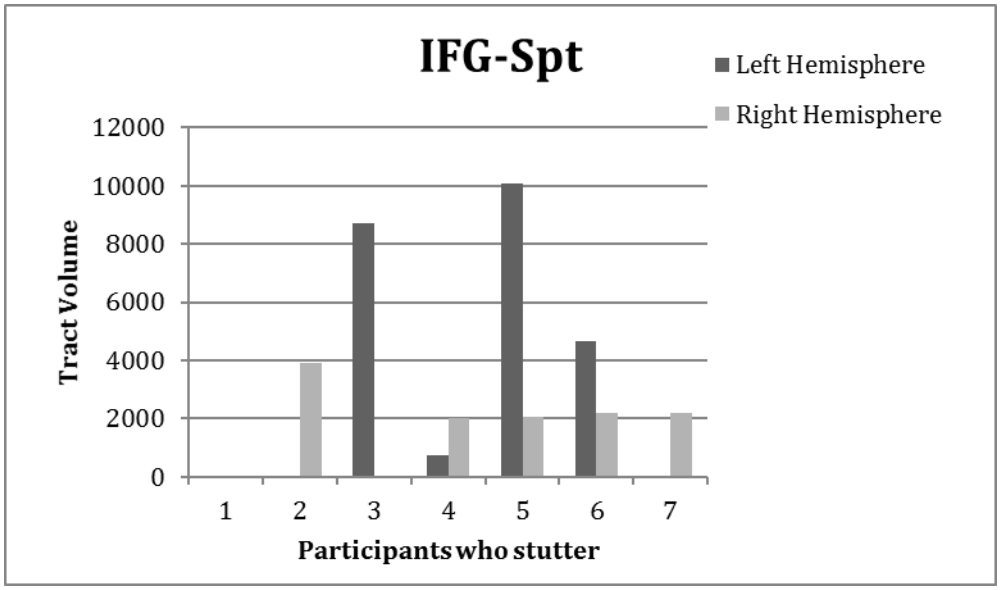


Figure 23: Tract volumes in left and right hemispheres of IFG-Spt in participants who stutter

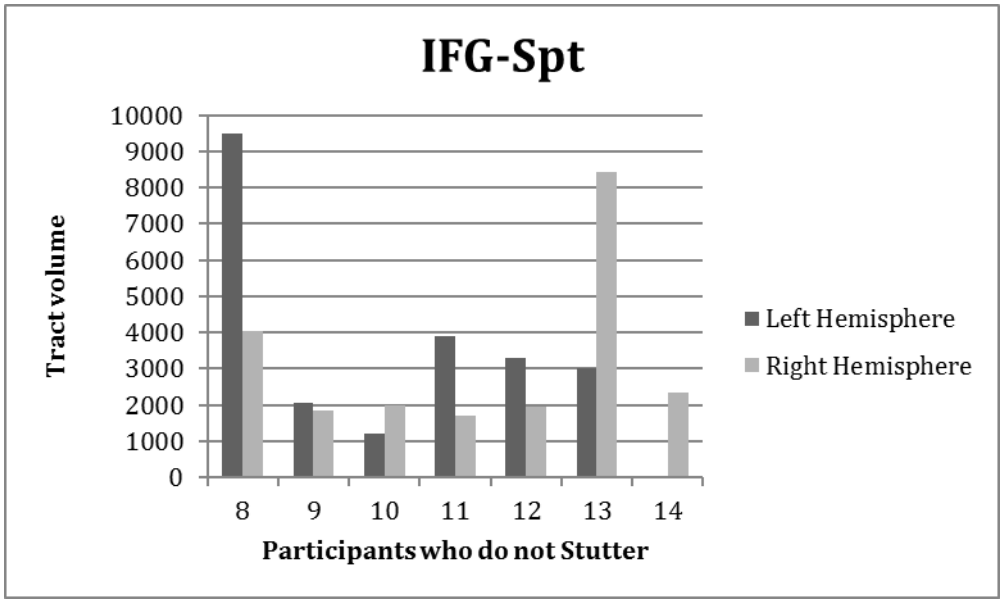


Figure 24: Tract volumes in left and right hemispheres of IFG-Spt in participants who do not stutter

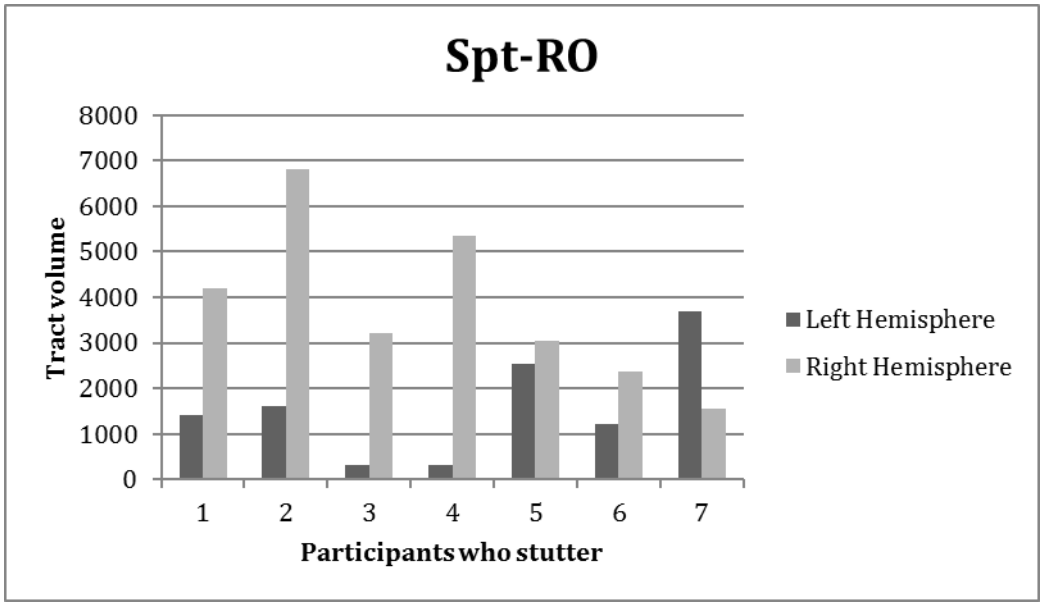


Figure 25: Tract volumes in left and right hemispheres of Spt-RO in participants who stutter

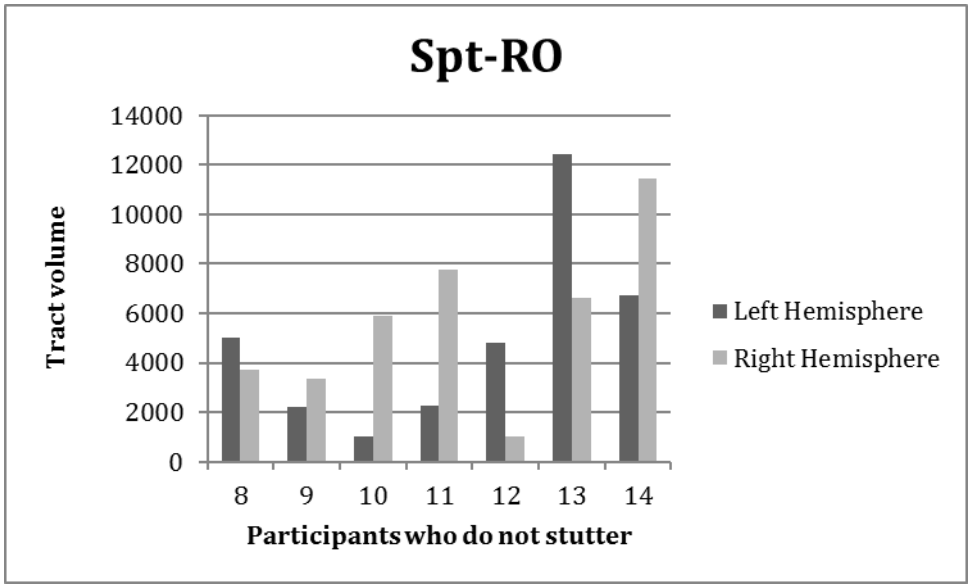


Figure 26: Tract volumes in left and right hemispheres of Spt-RO in participants who do not stutter

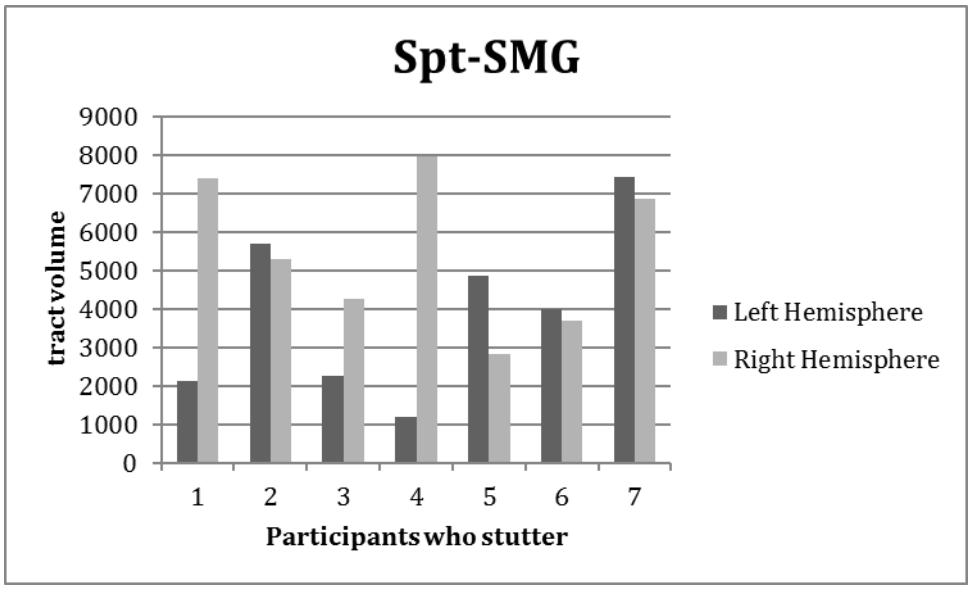


Figure 27: Tract volumes in left and right hemispheres of Spt-SMG in participants who stutter

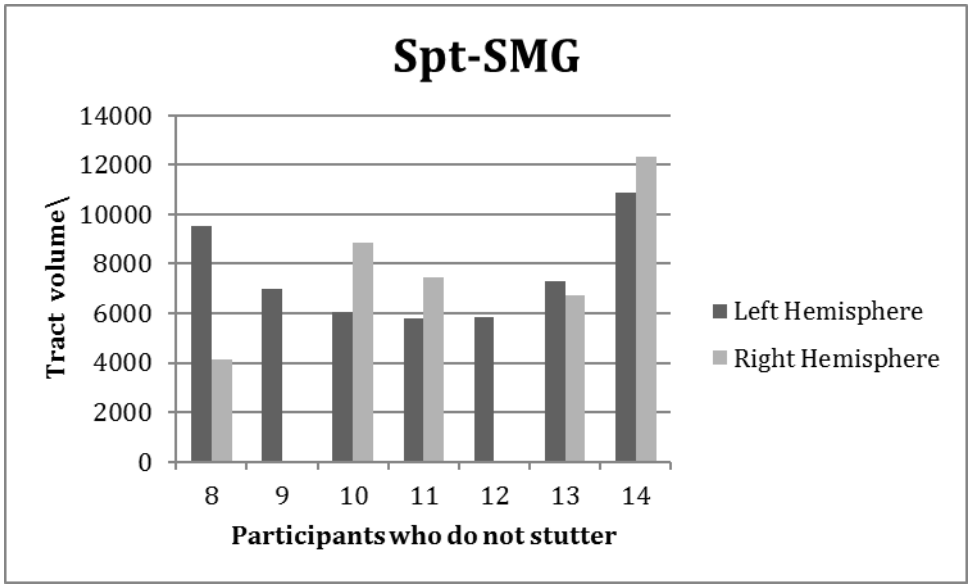


Figure 28: Tract volumes in left and right hemispheres of Spt-SMG in participants who do not stutter

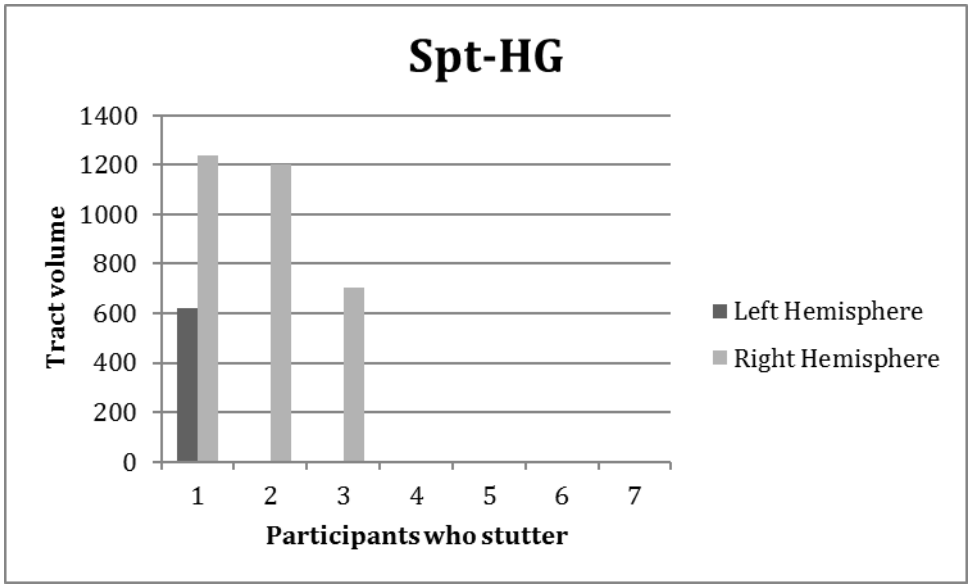


Figure 29: Tract volumes in left and right hemispheres of Spt-HG in participants who stutter

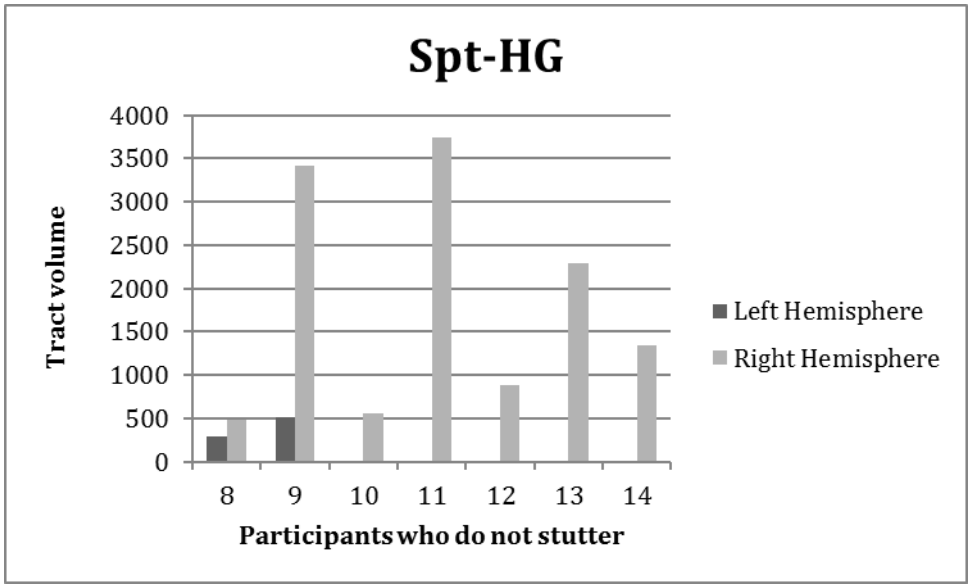


Figure 30: Tract volumes in left and right hemispheres of Spt-HG in participants who do not stutter

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