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NEUROCORRELATES OF SPEECH-MOTOR PLANNING AND EXECUTION IN
ADULTS AND CHILDREN WHO STUTTER

by

Bryan T. Brown

A thesis submitted in partial fulfillment
of the requirements for the Doctor of Philosophy
degree in Speech and Hearing Science in the
Graduate College of
The University of Iowa

December 2015

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CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

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has been approved by the Examining Committee for
the thesis requirement for the Doctor of Philosophy degree
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To the two people I wish most were here to see this day: Deborah Lee Paul-Brown and Christopher Richard Norman.

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Abstract

There is a rich literature demonstrating that adults who stutter (AWS) demonstrate atypical functional brain activity during speech production. These differences can be characterized by increased activity in the right inferior frontal gyrus and premotor regions and decreased activity in the left inferior frontal gyrus, premotor area, and bilaterally in the superior temporal gyrus. The process of speech production requires motor movements first be planned and then executed. However, few studies have examined activity related to speech-motor planning independently from speech-motor execution. Additionally, due to methodological limitations, few investigations have examined functional brain activity in children who stutter (CWS). We hypothesized that AWS and CWS would demonstrate atypical brain activity related to both speech-motor planning and execution. Using Near Infrared Spectroscopy (fNIRS), we measured the change in oxygenated hemoglobin concentration (HbO) during speech-motor planning (repetition of nonwords with three repeated or different syllables) and speech-motor execution (covert/overt naming). Results indicated that both AWS and CWS demonstrated cortical activity that was atypical during speech-motor planning processes in the right inferior frontal gyrus and atypical speech-motor execution processes in the left inferior frontal gyrus. Deactivations in the left inferior frontal gyrus may reflect inefficient feedforward mechanisms for speech production. Inefficient feedforward mechanisms will likely result in more variable movements, for which larger feedback correction signals will be necessary. Overactivations in the right inferior frontal gyrus may reflect this increased correction. Additionally, AWS demonstrated

atypical speech-motor planning activity in the right middle frontal gyrus, potentially related to the production of prosody. These results are presented within a theoretical framework of two competing theories of stuttering.

Public Abstract

From decades of research, one of the most consistent observations we have made about speech is that it is complicated. Our lips, tongue, jaw, vocal folds, and lungs must work together in a seamless dance of sounds, words and sentences. It's truly amazing that it all works together—and works together so quickly!

One of the ways it is able to work so quickly is because over the course of development our brains learn how to predict what movements are going to be necessary to produce the words we want to say. This prediction is followed up by a system that monitors errors in speech production. These two systems work together to form a highly precise and accurate method of producing speech. However, sometimes speech production breaks down. Developmental stuttering (or stuttering since childhood) is one of these ways speech production can break down.

Developmental stuttering is a communication disorder of childhood characterized by disruptions in the flow of speech. Speech requires movements; as such stuttering is undoubtedly a disorder of movement. However, when we move our brains must first plan the movements then the brain can carry out the movement. It is unclear if stuttering is related to atypical movement planning or atypical movement execution.

One of the ways we can measure this is through measuring brain activity during speech. There have been many attempts to measure brain activity related to stuttering. However, most of the current studies have two major flaws: they collect data from adults only and the tasks utilized did not examine speech-motor planning and speech-motor execution independently. Therefore, from these studies we do not

know if the differences observed are a cause or a consequence of stuttering and we don't know if the differences are related to the planning of speech or the execution of speech.

To answer both of these questions we asked 15 adults and six children who stutter (along with age- and gender matched peers) to perform two different speech tasks while we measured their brain activity. One task identified brain regions that were active when the planning of speech changed, but the execution did not. The second task identified brain regions that were active when speech execution changed but speech planning did not.

One of our main findings was that while adults and children who stutter showed similar differences during the execution of speech, they showed very different results during the planning of speech. Adults who stuttered showed many more differences in the planning of speech compared to the children. This suggests that while the differences in the execution of speech are fairly consistent across age groups, the planning of speech appears to change as children who stutter become adults who stutter.

Our study also revealed that adults and children who stutter may have a difficult time developing the precise predictions necessary for smooth speech movements. The left hemisphere inferior frontal gyrus is essential for these predictive movements, and in our study both adults and children who stutter showed decreased brain activity in this region. The right hemisphere inferior frontal gyrus is essential for the error monitoring. Similar with previous results, our study found that adults and children who stutter show increased activity in this region.

This suggests that the increased activity might be due to the need to make more corrections more frequently. When we consider both of these along with the fact that differences in the execution of speech (but not planning) are present from early on, it suggests that the differences in the development of the predictive aspect of speech production are the result of differences in the execution of speech and not the planning of speech.

The left inferior frontal gyrus is one of the important regions for speech production. People who don't stutter show more activity in the left inferior frontal gyrus during speech planning and speech execution. The results showed us that both adults and children who stutter showed atypical brain activity during speech planning and during speech execution. During speech planning adults and children who stutter demonstrated more activity in the right inferior frontal gyrus. This increased activity is thought to be compensating for reduced activity in the left inferior frontal gyrus. During speech execution adults and children who stutter demonstrated decreased activity in the left inferior frontal gyrus.

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Chapter 1: Introduction

Stuttering is a developmental disorder of speech that manifests primarily as repetitions and prolongations of sounds, syllables and words. The etiology of both stuttering onset and behavior continues to be debated in the literature, with contemporary theories implicating deficits in either speech motor planning or execution as the primary source. For example, theories that implicate interruption or delay of planning processes (e.g., Covert Repair Hypothesis; Postma & Kolk, 1993; and EXPLAN; Howell, AuYeung, 2002) hypothesize that moments or instances of stuttering arise when speech motor execution is initiated before the correct motor plan is completely assembled, resulting in speech movements that are either held (i.e. sound prolongation) or repeated (i.e. sound/syllable or whole-word repetitions) until the appropriate plan is available and selected. Alternately, theories of stuttering as a disorder of speech motor execution propose that unstable or insufficient feedback mechanisms underlie disruptions in speech production (Civier, Tasko, & Guenther, 2010; Max, Guenther, Gracco, Ghosh & Wallace, 2004).

Stuttering as a Disorder of Speech Motor Planning

Theories that implicate errors in speech-motor planning as the source of stuttering are based on models of normal language processing , primarily that of Levelt (1983, 1989). Levelt held that speech is the end result of a sequential, multi-step process that begins with the formulation of a mental concept into a series of lexical units and ends with the development and execution of an articulatory plan into speech movements. Speech output is monitored on-line for accuracy of both

message content and articulation (Postma, 2000). In their Execution and Planning theory of fluency control (EXPLAN), Howell & AuYeung, (2002) propose that both typical and stuttered disfluencies arise because varying segments of speech require different time intervals to plan and execute. This theory posits that a linguistic plan (composed of lexical units and appropriate phonology) must be complete before the articulatory plan is initiated. In the case of stuttered utterances, the execution of the articulatory plan precedes the completion of the linguistic plan, leading to “stalling” (through pausing, or repeating sounds, syllables, words or phrases) or advancing the articulatory plan (initiating what is available of the articulatory plan associated with the incomplete linguistic plan). In addition, Howell & AuYeung argue that individuals who stutter more frequently utilize an advancing strategy, thus leading to production of within-word more so than between word disfluencies.

As opposed to temporal discoordination of linguistic and articulatory plans, the Covert Repair Hypothesis (CRH; Postma & Kolk, 1993) utilizes Levelt’s notion of a monitoring system to propose that both normal and stuttered disfluencies emerge by way of a hypervigilant monitor that detects errors at multiple levels during assembly of both the linguistic and articulatory plans. When an error is detected, speech output is arrested to allow time for correction. Postma and Kolk argue that a hypervigilant monitor distinguishes individuals who stutter from their normally disfluent peers. The result is premature or inaccurate error detection leading to disruption in speech production to allow sufficient time for the prearticulatory error to be corrected; as such the central tenant of the CRH is that disfluencies are the by-products of prearticulatory speech errors.

Stuttering as a Disorder of Speech Motor Execution

Theories that implicate speech-motor execution as a source of disfluencies focus their attention on the role of feedback in the motor execution of an articulatory plan. In particular, negative feedback and feedforward control (i.e. Guenther, 2006) have both been implicated as sources of disfluent and stuttered speech. Negative feedback generates a correction to an ongoing system by comparing the system's actual output against expected output. If a correction is applied after the system has proceeded past the error the correction will be added when it is not necessary. As such a compounding correction signal is generated that will eventually cause the system to oscillate out of control. Feedforward control, on the other hand, utilizes previously learned commands to produce speech movements that are highly consistent but unable to be edited. Since speech is rapid and highly variable, utilizing either a negative feedback or feedforward control system alone is inadequate; speech-motor control for a system that is both rapid and accurate is achieved by the simultaneous use of both negative feedback and feedforward control (Guenther, 2006; Perkell, 2013). Given that there are two discrete methods of speech-motor control (e.g., negative feedback and feedforward motor control) the literature has postulated that each may contribute to breakdowns in fluent speech production. For example, a system that is over-reliant on negative feedback will begin to become inaccurate. In order to correct the compounding correction signal, speech production is arrested and initiated again (Civier et al., 2010). Alternatively, a system that has inefficient feedforward

commands will be inaccurate and be forced to rely more heavily on negative feedback (Max, et al., 2004).

Stuttering research has relied primarily on measurements of speech production to test theories that stuttering is related to errors in speech-motor planning or speech-motor execution. For example, linguistic errors and disfluencies are interpreted as evidence of deficits in speech-motor planning, while speech-motor execution has been examined by observing and measuring speech movements and the response to perturbation of incoming sensory stimuli. However, using peripheral measures of speech production cannot adequately compare speech-motor planning and speech-motor execution. Peripheral measures of speech production require speech to be produced. Speech-motor planning occurs prior to speech production, peripheral measures cannot observe speech-motor planning. As such, the competing theories have not been adequately compared. Neural imaging provides a tool to do so.

Since the late 1990s, advances in neural imaging techniques have allowed researchers to move beyond behavioral measurement to observe both cortical structure and function associated with speech production in adults who stutter (AWS). The earliest functional imaging studies in stuttering used Positron Emission Tomography (PET) to show that compared to adults who do not stutter (AWNS) during speech production AWS generated right lateralized activity in the primary motor cortex, dramatically increased activity in the supplementary motor area and right lateralization in the superior-lateral premotor cortex. Areas of deactivation

were also distinguishing, with AWS demonstrating reduced activity in the left superior temporal gyrus, the left inferior frontal gyrus and the left premotor cortex (Braun, Varga, Stager, Schulz, Selbie, Maisog & Ludlow, 1997; DeNil et al., 2000; DeNil et al., 2004; Fox, 1996; Ingham et al., 2000). In summary, unlike AWNS, who demonstrate brain activity that is lateralized to the left hemisphere, AWS demonstrate bilateral activity with somewhat reduced activity in the left hemisphere regions and increased in the right hemisphere regions. Reduced activity in left hemisphere regions, particularly in the left inferior frontal gyrus and premotor regions, may indicate reduced feed-forward models of speech production. Reduced feedforward commands may require increased reliance on incoming sensory and proprioceptive feedback (Civier, et al., 2010). Increased right hemisphere activity has thought to be compensatory in nature, rather than contributing to stuttering (Preibisch, Neumann, et al., 2003, Lu, Chen, et a, 2010). Compensatory activity from the right hemisphere may delay the assembly of the speech-motor plan or its execution. Timing delays have been proposed to contribute to stuttering in linguistic domains (Howell & Au-Yeung, 2004) as well as motor domains (Max, et al., 2003; Olander, et al., 2010).

More recent investigations of differences in brain activity between AWS and AWNS utilized functional magnetic resonance imaging (fMRI). Unlike PET, fMRI does not require an invasive, radioactive contrast agent. Researchers using fMRI to study brain activity during speech production in both AWS and AWNS have used a variety of tasks, including oral reading contrasted against silent reading (DeNil, et al., 2000), picture association (verb generation from noun) contrasted against picture labeling

(Blomgren, Nagarajan, Lee, Li, & Alvord, 2003), natural speech contrasted against choral speech (Fox, 1996), simulated stuttering in AWNS (DeNil et al., 2008), word repetition (Chang, et al., 2009), production of nonspeech-oral tasks (Chang, et al., 2009) and production of words of varying lengths (Lu, Chen, et al., 2010).

Regardless of speech task, the results of these studies revealed a robust and consistent observation: during speech production, AWS consistently show an increased activity in right hemisphere structures relative to AWNS. This atypical right laterality of brain activity associated with speech production has been observed in a number of regions, but among those most consistently reported are the right inferior frontal gyrus (Chang, et al., 2009; Ingham, et al., 2004; Lu, Chen, et al., 2010; Neumann, et al., 2003; Preibisch, Neumann, et al., 2003), right superior temporal gyrus (Chang, et al., 2009; DeNil, 2000; Ingham, 2004; Lu, 2010; VanBorsel, 2002), right precentral gyrus (Chang, et al., 2009; DeNil, 2000; Preibisch, Neumann, et al., 2003). Additionally, AWS demonstrated decreased activity in the left superior temporal gyrus (Chang et al., 2009; DeNil, et al., 2000) and the left inferior frontal gyrus (Chang, et al., 2009, Lu, Chen, et al., 2010). Among these cortical regions are those that support speech production. In particular, the left inferior frontal gyrus is associated with phonetic encoding (Papoutsis, deZwart, Jansma, Pickering Bednar & Horwitz, 2009), while the left superior temporal gyrus is part of the auditory association region of the temporal lobe which together with the inferior frontal gyrus forms a feedback loop for the evaluation of produced and perceived speech (Friederici, Ruschemeyer, Hahne & Fiebach et al., 2003). Together

these regions underlie the system for phonological encoding, perception and generating movements necessary for speech production.

Statement of the Problem and Purpose

While the results of imaging studies have advanced our understanding of the neurocorrelates of stuttering, critical issues remain in the identification of the role that speech motor planning and execution play in either the onset and development of stuttering, or in the production of stuttered speech. First, only two fMRI studies have experimentally parsed speech production into speech-motor planning and execution. Chang, et al., (2009) utilized a two-scanning procedure to determine neurocorrelates of speech-motor planning apart from execution. Second, only two studies to date have examined brain activity in preschoolers who stutter—one utilizing magnetoencephalography (MEG; Sowman, Crain, Harrison & Johnson 2014) and one using functional near infrared spectroscopy (fNIRS; Sato, et al., 2010). This literature is underrepresented despite the fact that stuttering is a developmental disorder that typically emerges between the ages of two and five years (Yairi & Ambrose, 1992a) and differences observed between AWS and AWNS most likely do not reflect the cause of stuttering (e.g. DeNil, et al., 2000), but rather neoplastic adaptations to the experience of stuttering.

Presently, relative to their adult counterparts little is known about functional brain activity in children who stutter during speech production. The difficulty of placing children in fMRI scanners is the primary reason for this—the scanner is a tightly enclosed space and the child is directed to move as little as possible. To

obtain functional brain activity data the child must then engage in a task in this rather unnatural environment. These reasons, in addition to the loud sounds of the magnet and high cost of fMRI data acquisition, result in a procedure that is untenable for most children.

There are two challenges to moving forward in our understanding of the neurocorrelates of speech production in those who stutter. First, we need to be able to isolate the two components of motor activity: planning and execution, in order to assess the validity of contemporary theories of stuttering that hinge on each. Second, we need to use imaging techniques that are suitable for adults as well as children, so that we can elucidate both the neurocorrelates of chronic stuttering, and those that underlie the onset and development of the disorder. The relatively recent addition of fNIRS to the options of measuring brain activity provides such a method.

The purpose of the current study was to examine the cortical activity associated with speech motor planning and execution in both children and adults who stutter using fNIRS, a methodology which allows for the evaluation of cortical activity through measurement of changes in the concentration of oxygenated hemoglobin. To isolate speech-motor planning and speech-motor execution we designed two tasks: each designed to isolate cortical activity associated with either speech-motor planning or speech-motor execution. The speech-motor planning task was adopted from Lu, Chen et al., (2010), and involved two types of nonwords that contained similar levels of motor execution (three syllables) but had different levels

of motor planning (one syllable repeated three times or three different syllables). The speech-motor execution task was adopted from Chang, et al., (2009), and involved two types of naming tasks that had a similar level of motor planning (one word) but had different levels of motor execution (no execution, or execution).

These tasks were used to evaluate cortical activity related to speech-motor planning and speech motor execution in AWS and AWNS as well as CWS and CWNS. By examining regions that show a significant change in activity between these conditions we were able to isolate cortical regions associated with speech-motor planning and execution in both adult and pediatric populations with the aim to answer the following questions:

1. Can fNIRS be used to replicate previous findings from fMRI studies showing that compared to AWNS, during speech production and language processing, AWS have increased activity in right hemisphere inferior frontal gyrus and superior temporal gyrus , and decreased activity in left hemisphere superior temporal gyrus.
2. Do AWS and CWS demonstrate differences in cortical activity associated with speech-motor planning and execution relative to AWNS and CWNS?
3. Do AWS and CWS demonstrate similar differences in cortical activity associated with speech-motor planning and execution?

Chapter 2: Literature Review

This chapter is organized into five sections. The first section describes the disorder of developmental stuttering. The second section describes theoretical models of stuttering that implicate motor processes as a source of disfluencies. The third section reviews research examining speech motor processing in individuals who stutter. The fourth section reviews research describing the neurophysiology of stuttering. Finally, the fifth section introduces near-infrared spectroscopy (fNIRS) as a tool for observing and measuring cortical activity during speech production in children who stutter.

Developmental Stuttering

Stuttering is a speech disorder beginning in early childhood, between two and five years of age. Stuttering is characterized by breakdown in the timing of speech movements. These breakdowns present behaviorally as two main classes of disfluencies: stuttering-like disfluencies (SLDs) and normal disfluencies (NDs). SLDs consist of a disruption in transitioning between phonemes *within* word boundaries, and typically present as sound and syllable repetitions, and audible and inaudible prolongations. NDs consist of a disruption in transitioning *between* word boundaries. These disfluencies include phrase repetitions, interjections and revisions (Bloodstein & Bernstein Ratner, 2008; Bloodstein, 1958; Johnson, 1959; Van Riper, 1982; Yairi & Lewis, 1984).

Stuttering emerges relatively late, typically between the ages of two and five years during periods of rapid expansion of the child's language abilities (Mansson,

2000; Yairi & Ambrose, 1992a, 1992b, 1999, 2005; Yairi, 1983). Longitudinal studies indicated that the onset of stuttering is not associated with a single attribute; rather a combination of attributes may increase the likelihood of stuttering onset (Paden & Yairi, 1996; Watkins & Yairi, 1997; Yairi & Ambrose, 1999). These attributes span multiple domains including genetic, environmental, motoric and linguistic. Children are more likely to develop stuttering if they have a family history of stuttering (Howie 1981, Kidd, Kidd & Records, 1978, Kloth et al., 2000), have reduced oro-motor skills (Kelly, et al., 1995; Riley & Riley, 1980), slower reaction times (Bishop et al., 1991) and reduced control of laryngeal movements (Conture et al., 1986). Reduced phonological abilities have also been associated with increased likelihood of stuttering onset (Blood, et al., 2003; Louko, et al., 1990; Paden, et al., 1999; Pellowski, et al., 2000).

The nature of relationship between stuttering and language remains unclear. The onset of stuttering has been associated with subtly reduced (but within normal limits) language abilities (Anderson & Conture, 2001, Byrd & Cooper, 1989, Ratner & Silverman, 2000, Ryan 1992, Silverman & Ratner, 2002) and subtly increased language proficiency (Rommel, 1999, Watkins & Yairi, 1999). Still others have found no discrepancy regarding language ability (Kloth et al., 1995, 1998).

Language proficiency is not the only feature of language that affects stuttering. Moments of stuttering are more likely to occur in longer and syntactically complex utterances (Bernstein Ratner & Sih 1987; Gaines, Runyan, & Meyers, 1991; Kadi-Hanifi & Howell, 1992; Melnick & Conture, 2000). This may be due to the increased linguistic demand; however, these longer and more syntactically complex

utterances also result in more complex motor movements (Kleinow & Smith, 2000; Manor, Smith & Grayson, 2000; Smith & Goffman, 1998) calling into question the interface between motor ability and language proficiency.

This motor and language interface is particularly interesting given that a majority of preschool children who stutter will experience unassisted recovery (Mansson, 2000; Yairi & Ambrose 1992a, 1999). Motor ability and language proficiency are developmental skills that are acquired simultaneously. The fact that both language proficiency and motor ability are risk factors for the development of stuttering may indicate that the increased risk of stuttering from each is not directly due to language proficiency and motor ability in isolation. Rather, the driving force regarding the relationship between stuttering, language proficiency and motor ability is a mismatch between language proficiency and motor ability skills. For children who recover from stuttering, recovery may potentially be achieved through an equalization of the skills mismatch.

Approximately 75% of preschool children who stutter will experience unassisted recovery (Yairi & Ambrose 1992a). Recovery typically occurs between 6 and 36 months after onset (Mansson, 2000; Yairi & Ambrose, 1992a, 1999). At stuttering onset the gender ratio is nearly 1 (Kloth et al., 1999; Yairi, 1983), however, female children are more likely to recover, leading to a disproportionate gender ratio ranging from 3:1 to 6:1 (Ambrose, Yairi, & Cox, 1993; Bloodstein & Bernstein Ratner, 2008; Gregg & Yairi, 2012; Mansson, 2000; Reilly et al., 2009; R. V Watkins & Yairi, 1999; Yairi, Ambrose, Paden, et al., 1996; Yairi & Ambrose, 1992a, 1992b). As such, gender appears to be a risk factor for persistence. Other factors

that contribute to the likelihood of persistence include reduced phonological accuracy (Paden, Yairi, & Ambrose, 1999; Paden & Yairi, 1996; Ryan, 1992; Throneburg, Yairi, & Paden, 1994), a more reactive temperament (Anderson, Pellowski, Conture, & Kelly, 2003; Bloodstein & Bernstein Ratner, 2008; Eggers, De Nil, & Van den Bergh, 2010; Kefalianos, Onslow, Block, Menzies, & Reilly, 2012), environmental factors including parent anxiety (Douglas, 2005; Zenner, Ritterman, Bowen & Gronhovd, 1978), and child's awareness of and negative reaction to his own stuttering (Ambrose & Yairi, Ambrose, Paden, & Thronebug, 1994, Ezrati-Vinacour, Platzky & Yairi, 2001; Vanryckeghem, Brutten & Hernandez, 2005; Vanryckeghem & Brutten, 1997).

While the literature regarding the onset and development of stuttering is growing, the vast majority of data regarding speech-motor differences between stuttering and non-stuttering speakers comes from adults. Relative to AWNS, AWS demonstrate speech movements that show evidence of decreased coordination between the articulation, respiratory and phonatory systems (Baken and Cavallo 1983; Hixon, 1973) and more variable articulatory movements (Kleinow and Smith, 2006). These studies of speech production have greatly contributed to the theoretical understandings of stuttering.

The study of group differences between stuttering and normally fluent populations among these contributing factors has led to a number of hypotheses of stuttering onset and development. Given that stuttering is a disorder that impacts speech movements, of particular interest are theories that implicate speech motor control.

Theoretical Models of Stuttering that Implicate Motor Control

The idea that stuttering is a disorder of speech-motor production is neither new nor controversial. The stuttering literature is rich with evaluations of perceptually fluent speech production indicating that AWS, CWS and PCWS demonstrate different strategies for the organization of speech production. These data come from kinematic, electromyography, and acoustic evaluations of perceptually fluent speech movements. Thereby suggesting that disfluencies are not merely isolated events, but that the speech motor system of AWS, CWS and PCWS demonstrates persistently atypical movement strategies. The ubiquity of atypical strategies of speech movements have lead some researchers to conclude that the speech motor system of AWS, CWS and PCWS is relatively uncoordinated compared to their fluent counterparts.

Speech movement is not the only domain in which AWS and CWS demonstrate atypical movement strategies. During finger tapping and bimanual clapping tasks AWS and CWS routinely demonstrate increased variability during these non-speech fine-motor tasks including finger tapping and clapping (Hulstijn, Summers, van Lieshout & Peters, 1992; Olander, Smith, & Zelaznik, 2010; Zelaznik, Smith, Franz, & Ho, 1997). These data suggest that the motor impairment underlying stuttering may not be specific to the speech-motor system, but may be a pervasive timing disorder of the motor system that has such a high threshold that speech is the only motor task with high enough temporal demands to consistently surpasses the threshold.

There are several contemporary theories that implicate breakdowns in both speech- and nonspeech-motor control as the cause of stuttering. These theories fall into two broad categories: those that address the onset and development of stuttering and those that address the moment of stuttering (Bloodstein & Bernstein Ratner, 2008).

Theories of Onset and Development.

Multifactorial Model.

One of the most well-known and widely accepted theories of stuttering posits that stuttering emerges from a dynamic, multifactorial process that is influenced by a number of factors, including genetics (Ambrose & Cox, 1997; Andrews, Morris-Yates, Howie, & Martin, 1991; Felsenfeld, et al., 2000; Yairi, Ambrose, & Cox, 1997), parental language input (Kasprisin-Burrelli, Egolf, & Shames, 1972; Miles & Bernstein Ratner, 2001), temperament (Anderson et al., 2003; Eggers et al., 2010; Eggers, De Nil, & Van den Bergh, 2013), language and linguistic demands (Buhr & Zebrowski, 2009; Maner, Smith, & Grayson, 2000; Weber-Fox, Hampton Wray, & Arnold, 2013), motor status (Dokoza, Hedeveer, & Sarić, 2011; Maner et al., 2000; Olander et al., 2010) and the interaction of linguistic and motor demands (Smith & Goffman, 2004). In their Multifactorial Model of Stuttering, Smith and Kelly (1997) proposed that stuttering is the manifestation of a constellation of factors that interact in a complex fashion to increase the likelihood of stuttering onset. These factors need not be consistent between individuals, but rather each child presents with a unique constellation of *risk factors* that contribute in different proportions to both the emergence and development of the disorder. Each constellation reflects an

index of the likelihood of stuttering persistence or recovery that is based on the individual factors included within the constellation. Accordingly, research has shown that the PCWS who recover are likely to be female (Mansson, 2000; Reilly et al., 2009; Yairi & Ambrose, 1999), be without a family history of stuttering (Ambrose & Cox, 1997), have developmentally appropriate articulation abilities (Paden, et al., 1999) and developmentally appropriate language abilities (Watkins & Yairi, 1997).

One factor in the Multifactorial Model that is thought to contribute to stuttering onset and development is the status of the child's speech-motor control abilities. Analysis of speech production indicate that PCWS are similar to CWNS with regard to the coordination of respiratory, articulatory and phonatory events during speech production (Caruso, Conture, & Colton, 1988), voice onset time (Cullinan & Springer, 1980), duration of speech acoustic events (Zebrowski, Conture, & Cudahy, 1985), diadochokinetic rate (Yaruss & Logan, 2002) speaking rate (Hall, Amir, & Yairi, 1999), and duration of disfluencies (Yairi & Hall, 1993; Zebrowski, 1991). The key differences between the motor abilities of PCWS and PCWNS emerge as a consequence of the interaction between language and motor demands. In both preschool-age children, school-age children and adults movement consistency across repeated productions of similar motor gestures changes with linguistic complexity (Kleinow & Smith, 2000, 2006; Maner et al., 2000; Smith & Goffman, 2004). For PCWS, CWS and AWS increases in linguistic complexity result in a decrease in consistency of repeated productions (Kleinow & Smith, 2000; Maner et al., 2000; Smith & Kleinow, 2000). PCWS, CWS and AWS alike demonstrate further

reductions in movement consistency of bi-labial approximations during repeated productions as linguistic demands increase. The reduction in motor consistency across linguistic contexts may be driven by subtle deficits in the motor systems of people who stutter given that participants were all within normal limits on standardized measures of language ability.

If the movement of speech structures changes with linguistic complexity it follows that the planning and or execution of those motor events also varies with linguistic complexity. It remains unknown whether the relationship between motor consistency and linguistic complexity is a result of aberrant speech-motor planning, execution or their interface.

Variability Model.

The Variability Model (V-Model) proposed by Packman, et al., (1996, 2000, 2004) describes onset of stuttering from a developmental perspective. It posits that variable linguistic demands on speech production (e.g., syllabic stress) increase the necessary complexity of the speech-motor plan. Working from the assumption that individuals who stutter have a motor system that is more susceptible to breakdown, the increased complexity of the motor plan exceeds the ability of the motor execution system to generate the planned movements. When this occurs the motor execution system temporarily reduces the complexity of the speech motor plan in an attempt to allow more time for the motor execution system to generate the motor commands. These reductions in complexity take the form of sound/syllable repetitions and prolongations. Thus, according to the V-Model, disfluencies are a stalling strategy.

Empirical support for this theory comes from the increase of speech fluency when speech syllables are produced with equal stress (Packman, Onslow, Richard, & Van Doorn, 1996) and the previously reported kinematic data indicating that both AWS, CWS and PCWS show increased variability of speech movements relative to fluent peers. This model predicts that the planning of speech motor events is intact in stuttering but breakdown occurs as a result of deficiencies in speech motor execution. Therefore, the speech motor execution system, and not the motor planning system, is complicit in the onset of stuttering, and evidence of stuttering at the cortical level should be evident in speech-motor execution whereas, speech motor planning should be similar between stuttering and fluent populations.

Theories of the Moment of Stuttering.

Covert Repair Hypothesis.

The Covert Repair Hypothesis (CRH) posits that disfluencies arise as a result of improper selection of phonemes during the planning of speech production (Bloodstein & Bernstein Ratner, 2008; Postma & Kolk, 1993). This theory is based on Levelt's model of language production (Levelt, 1983, 1989). Levelt's model of language asserts that language production is the serial processing of linguistic information whereby the phonetic plan of speech production is passed through a monitor to verify the correct phoneme selection. If an error in the phonetic plan is detected the monitor arrests speech production until the error is corrected. Thus, according to Levelt's model disfluencies are a delay tactic to ensure proper speech-motor planning. The CRH extends Levelt's model to suggest that in stuttering the monitor is hyper-vigilant—it detects errors in the phonetic plan where none are

present. This results in a greater proportion of disfluencies than is observed in people who do not stutter.

It is important to note that it is the planning of speech production that is thought to lead to fluency breakdown. As such, cortical evidence of stuttering should be evident in aberrant speech motor planning. Speech motor execution, on the other hand, should be similar between stuttering and fluent populations.

EXPLAN.

In contrast to the CRH, the EXPLAN Theory of Fluency Control (Howell & Au-Yeung, 2002) posits that disfluencies are caused by misalignment in the serial ordering of both word level planning (**EXPLAN**) and execution (**EXPLAN**) of speech. It is not phoneme selection that interrupts fluency production (as in the case of CRH) but it is the planning of the muscle commands to generate the phonemes that cause the disruption. In this theoretical model of fluency breakdown, the planning and execution of words are independent events.

EXPLAN predicts that motor planning and motor execution are two independent, simultaneous processing streams whereby the execution stream is delayed from the planning stream by one word. Breakdowns in fluency arise when the planning of an utterance (PLAN) is not completed prior to the beginning of execution (EX) (Execution, then, precedes planning and is the underlying concept for the theory's title, EXPLAN). As the delay between the planning and execution processing streams decreases, at some point the speaker will encounter an execution event that is not sufficiently planned. In this case, the authors posit two broad types of corrections that can be made. Howell and Au-Yeung use the terms

'stalling' and 'advancing' for these corrections; however, these two types of correction are synonymous with normal disfluencies and stuttering-like disfluencies respectively.

In the case of stalling corrections (correction resulting in normal disfluencies) the speaker returns to a previously planned event and reproduces it in an effort to provide sufficient time for the completion of planning, thus allowing speech production to continue. According to EXPLAN, planning and execution occur at the word level, so the stalling correction returns a correction that contains at least one whole word resulting in disfluencies that occur between word boundaries. Stuttering-like disfluencies are similarly used in an attempt to allow sufficient time for the plan to complete; however, instead of reproducing previously planned events, the current execution is sustained. Thus, the advancing correction returns a correction containing less than one whole word, resulting in corrections that occur within word boundaries.

Stuttering as Disorder of Impaired Speech-Motor Control.

Accurate and expedient speech production relies on two main forms of motor control: negative feedback and feedforward motor control. Negative feedback utilizes incoming acoustic and proprioceptive feedback; while feedforward motor control utilizes previously learned movement patterns to produce movements. A negative feedback system of motor control is a slow process that allows for online correction of motor movements. Feedforward motor control is a rapid process that allows for rigidly consistent motor movements. Both are necessary in order to make online changes to speech production.

Evidence of acoustic feedback comes in the form of slips of the tongue that are corrected more quickly than reaction time would allow voluntary correction to occur as well as changes to fundamental frequency during altered frequency feedback (Feng, Gracco, & Max, 2011). Evidence of proprioceptive feedback comes in the form of adjustments to speech movement gestures in response to perturbations (Abbs, Gracco, & Cole, 1984; Abbs & Gracco, 1984; Feng et al., 2011; Folkins & Zimmermann, 1982; Kelso, Tuller, Vatikiotis-Bateson, & Fowler, 1984; Namasivayam, van Lieshout, & De Nil, 2008). The process of planning and executing motor behaviors relies on the integration of incoming acoustic and proprioceptive feedback.

Incoming feedback is not the only way dynamic changes are made the speech mechanism; to accommodate the rapid pace at which speech occurs, the speech production system utilizes a predictive feed-forward mechanism of motor control (Dhanjal, Handunnetthi, Patel, & Wise, 2008; Guenther, Ghosh, & Tourville, 2006; Guenther, Hampson, & Johnson, 1998). Stuttering has been hypothesized to result from a disruption in this motor control process. This disruption occurs either as an overreliance on incoming feedback or a weak feedforward mechanism (Civier, Tasko, & Guenther, 2011; Max et al., 2004; Namasivayam et al., 2009; Namasivayam & van Lieshout, 2008)

A reliance on incoming feedback will result in a motor system that has the potential to oscillate out of control—as negative feedback loops are prone to do. In negative feedback loops a feedback sensor detects the difference between the expected movement (speech-motor plan) and the detected movement

(proprioception). The ongoing motor commands are then adjusted, by subtracting the error (thus the *negative* feedback loop) to correct the error. This process requires time to complete. The error must be detected and then subtracted from future iterations. This works well for relatively slow cycles (e.g., walking); however, if the movement is rapid (e.g., speech production) the correction will arrive late, potentially compounding the error.

In contrast, feedforward mechanisms rely on predicted motor expectations. The feedforward system takes no account of the current status of the system—the same movement is applied regardless of the starting position of the system. This results in a rapid, but inaccurate system. The solution to this is to integrate feedback and feedforward controls to provide the motor system with trajectory expectations to rapidly plan (feedforward) movements and the sensory information (feedback) to evaluate the accuracy of the plan's execution—this is the mechanism for dynamic motor control utilized by the speech-motor system.

In the case of stuttering, disfluency may be the result of a correction signal that arrives too late, resulting in a breakdown of the forward flow of speech. Alternatively, disfluency could be the result of inaccurate feedforward predictions. The commonly held hypothesis is that stuttering is an overreliance on feedback. This comes from work demonstrating that AWS are slow to respond to perturbations to speech gestures (Namasivayam et al., 2008) and computational models of speech production that produce repetitions and prolongations when dependence on acoustic feedback is increased (Civier et al., 2011). Anecdotal support comes from the clinical evidence that stuttering frequency decreases in the

presence of altered auditory feedback (Kalinowski et al., 1993; Lincoln, Packman, & Onslow, 2006). While speaking under altered auditory feedback the incoming acoustic feedback is unreliable, therefore, it is suggested that AWS rely more on the feedforward mechanisms of motor control.

There remain several open questions regarding the theoretical basis of stuttering. The literature has yet to determine whether stuttering results from mismatched language and motor abilities, improperly sequenced phonetic and motor plans, inefficiently controlled speech movements or a combination of factors.

Research in Speech-Motor Processing

Speech is spontaneously and independently generated, therefore, movements for speech production must first be planned and executed. There are multiple ways to measure speech-motor processing that range from proximal (cortical activity) to distal (speech production) measures. Methods commonly include analysis of the acoustic speech signal, examination of muscle activity, and analysis of the kinematic movements of the articulation, respiratory and laryngeal subsystems of speech production. In recent years, the examination of the neurophysiology of speech production has become possible. These methods include transcranial magnetic stimulation, fMRI and near-infrared spectroscopy (NIRS). These data have been essential in the formulation of current theoretical models of speech production including neural networks.

Neural network model of speech motor control.

A commonly accepted neural network describing regions of cortical activity associated with the planning, execution and integration of feedback during speech

production and is the Directions Into the Velocities of Articulators (DIVA) Model (Guenther et al., 2006; Guenther & Perkell, 2004; Guenther, 2006; Terband, Maassen, Guenther, & Brumberg, 2009; Tourville & Guenther, 2011). The DIVA model integrates auditory and somatosensory feedback into the motor network for the neural control of speech production to produce a model of the development of speech-motor skill acquisition. This model demonstrates the capacity to learn the process of speech production from acoustic models by the integration of auditory and somatosensory feedback to feed forward predictions of speech (phonological) targets. The model contains a set of articulators with the ability to manipulate acoustic output roughly equivalent to manipulations to place, manner and voicing of articulation. The model's output begins as a babbling phase and through a learning phase advances to conventional word production (Guenther et al., 2006; Guenther & Perkell, 2004).

The DIVA model postulates that the speech motor control system integrates neural regions associated with feed forward mechanisms for motor movements with neural regions responsible for integrating auditory and somatosensory feedback. By changing the dependence of the model on feed forward and feedback systems the DIVA model can simulate neural activity thought to contribute to communication disorders including acquired apraxia of speech (Maas, Mailend, & Guenther, 2013), childhood apraxia of speech (Terband et al., 2009) and stuttering (Civier et al., 2011).

The feed forward and feedback mechanisms of motor control included in the DIVA model are proposed to be associated with specific tasks, or maps, as the

original authors describe. These maps that combine to create the DIVA model are divided into a feed forward control mechanism and a feedback control mechanism. See Figure 1 for a schematic of the DIVA model. The feed forward control mechanism includes a Motor Initiation map, that sends input to the Articulator Velocity and Position maps. The Articulator Velocity and Position map integrates feed forward commands from the Speech Sound map to generate the motor commands for speech production. During the process of speech production, acoustic and somatosensory feedback are generated and available to the feedback system.

The feedback system consists of incoming information about the state of the acoustic signal as well as proprioceptive information about the position of articulators. This information is encoded in the Auditory State Map and Somatosensory State Map respectively. During speech production the Speech Sound Map sends acoustic and somatosensory feed forward information to the Auditory Target Map and Somatosensory Target Map respectively. For both acoustic and somatosensory systems, input from the Target Map is compared to the State Map in the Error Map. The Auditory and Somatosensory Error Maps send information about the difference between the target and state of the acoustic and somatosensory system to the Feedback Control Map that generates feedback commands that edit the motor commands generated by the Articulator Velocity and Position maps.

Figure 1 presents a schematic of the DIVA model including the maps that comprise the feed forward and feedback loops. DIVA is made biologically plausible by the assignment of maps to cortical regions that, based on fMRI evidence, are associated with the tasks the map completes. The Speech Sound Map is theorized to

be in the posterior inferior frontal gyrus. The Speech Sound Map is the source of speech-motor planning. The inferior frontal gyrus contains a repository of phonological targets, from this repository a phonetic plan for word production is assembled. This phonetic plan and an error correction plan, from the Feedback Control Map in the right ventral premotor area and right posterior inferior frontal gyrus, are combined into motor execution commands in the Articulator Velocity and Position Maps, located in the ventral Motor Cortex. The integration of articulatory velocity and position maps have been hypothesized to be of particular importance to the development of speech and in the development of stuttering (Civier, et al., 2010; Tourville, et al., 2006) The Feedback Control Map, responsible for integrating the difference between expected and observed auditory and somatosensory information, generates the error correction plan.

Using this figure we can determine cortical and subcortical regions associated with the planning and execution of speech production as well as the processing of acoustic and somatosensory feedback. The execution of speech production, like all voluntary movement, relies on the disinhibition of the basal ganglia and the activation of the Articulator Velocity and Position Maps. Therefore, activity related to speech motor execution should be observed in the supplementary motor area (SMA), relative to the initiation of movement, and the ventral primary motor cortex, relative to the position displacement and speed required of the articulators. Activity related to the planning of speech movements integrates the error signal from the feedback system into the expectations of articulator movements based on the phonetic plan. In the case of altered auditory feedback

during speech production consisting of altered first or second formant frequencies, the difference between the expected vowel and the observed vowel is processed in the posterior superior temporal gyrus bilaterally as well as right hemisphere prefrontal and rolandic cortices (Tourville, Reilly, & Guenther, 2008). Regions generating the auditory error signal send projections to the right primary motor cortex and inferior frontal gyrus. These connections demonstrated increased activity during the altered feedback condition suggesting an auditory feedback control network (Tourville et al., 2008).

A right hemisphere auditory feedback control network is particularly interesting given that stuttering has been hypothesized to result from an over-reliance on auditory negative feedback during speech (Civier et al., 2011; Max et al., 2004; Namasivayam et al., 2009) and relative to AWNS, AWS demonstrate increased right inferior frontal gyrus activity during speech production (Chang et al., 2009; De Nil et al., 2001; Lu, Chen, et al., 2010; Lu, Peng, et al., 2010; Neumann et al., 2003; Preibisch, Neumann, et al., 2003; Preibisch, Raab, et al., 2003). This may reflect a mechanistic explanation for atypical cortical laterality during speech production in AWS; however, this mechanism does not indicate whether the development of atypical laterality is related to the development of stuttering.

Laterality of Brain Activity Related to Language.

From the earliest investigations of the brain's contribution to language, the left hemisphere's role has dominated the discussion. Early accounts of language laterality from lesion studies in adults indicate that the cortical control of language is located in the left hemisphere. In children, however, more recent fMRI

evaluations indicate that the left hemisphere may not be innately specialized for the control of language. Young children with lesions in left hemisphere regions associated with language deficits in adults develop language abilities that are largely within normal limits (Alajouanine & Lhermitte, 1965; Aram & Ekelman, 1986; Aram, Meyers, & Ekelman, 1990; Dennis & Kohn, 1975; Ewing-Cobbs & Barnes, 2002; Feldman, Holland, Kemp, & Janosky, 1992; Hécaen, 1976; Kohn, 1980; Levy, Amir, & Shalev, 1992; Rasmussen & Milner, 1977; Riva & Cazzaniga, 1986; Thal et al., 1991; Woods & Teuber, 1978; Wulfeck, Trauner, & Tallal, 1990). These children show brain activity in right hemisphere homologues suggesting a compensatory role of right hemisphere homologues. Similarly, children with benign rolandic epilepsy foci in the left hemisphere rolandic region show language activity in the right hemisphere. In contrast, controls and children with epileptic foci in the right hemisphere showed typical, that is left, language laterality (Kohn, 1980; Piccirilli, D'Alessandro, Tiacci, & Ferroni, 1988; Rasmussen & Milner, 1977; Riva & Cazzaniga, 1986; Vargha-Khadem, Isaacs, Papaleloudi, Polkey, & Wilson, 1991; Vargha-Khadem, O'Gorman, & Watters, 1985). This atypical language laterality observed in brain-damaged children suggests that each hemisphere shows some equipotentiality for language.

The equipotentiality of the hemispheres for language is observed early in development in typically developing children. Imaging studies of the development of brain activity related to language in typically developing children demonstrate that the dominance of the left hemisphere for language is a developmental specialization process—young typically developing children show more right hemisphere activity

during language tasks than older typically developing children and adults (Holland, et al., 2001; Szaflarski, Holland, Schmithorst, & Byars, 2006).

Hemispheric specialization is not static throughout the lifespan. There are age-related reductions in brain activity associated with the left hemisphere specialization for language. This is true not only before language proficiency is acquired, but after as well (Dolcos, Rice & Cabeza, 2002). According to the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) Model (Cabeza, 2002) this retreat from left hemisphere specialization has two potential mechanistic hypotheses: compensation to counteract age-related neurocognitive decline or a dedifferentiation of language related networks in the brain, potentially reflecting global or regional neural reorganization.

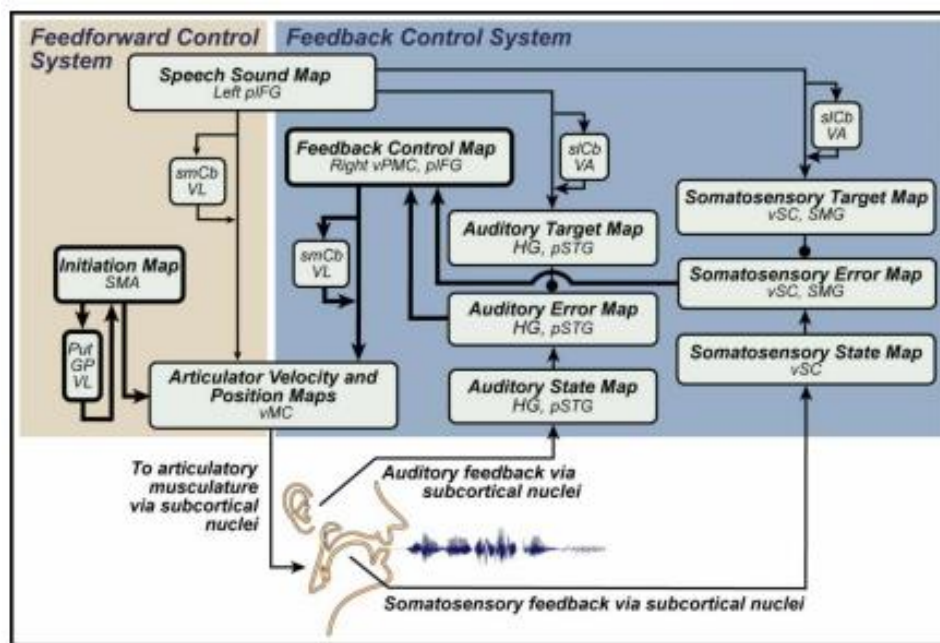


Figure 1 Schematic of the DIVA model.

Abbreviations: GP = Globus Pallidus, HG = Heschl's Gyrus, pInferior frontal gyrus = posterior Inferior Frontal Gyrus, pSuperior temporal gyrus = posterior Superior Temporal Gyrus, Put = Putamen, smCb = superior medial Cerebellum, SMG = Supramarginal Gyrus, VA = Ventral anterior nucleus of the Cerebellum, VL = Vento Lateral nucleus of the Thalamus, vMC = ventral Motor Cortex, vPMC = ventral Premotor Cortex, vSC = ventral Somatosensory Cortex (Tourville & Guenther, 2009, p. 95. The DIVA model: A neural theory of speech acquisition and production. *Language and Cognitive Processes*).

This reduction in hemispheric asymmetry for language processing is consistent with other domains of age-related changes in cognitive function including episodic memory encoding and retrieval. The prefrontal cortex (PFC) is associated with activity related to encoding and recall of personally experienced past events (episodic memory). In younger adults, activity is localized to the left hemisphere PFC during encoding and on the right hemisphere during retrieval (Cabeza & Nyberg, 2000); an established pattern referred to as the hemispheric encoding/retrieval asymmetry (HERA; Nyberg, Cabeza and Tulving 1996, 1998; Tulving, Kapur Craik, Moscovitch, & Houle 1994). The HERA does not hold true for older adults, who display bilateral activity in the PFC during word recall rather than the right hemispheric activity their younger counterparts display (Cabeza, Grady 1997). This bilateral PFC activity in older adults is also observed during word stem cued-recall (Bachman, 1997) and word recognition (Madden, Turkington, Provenzale, Denny, Hawk, Gottlob & Coleman, 1999)—an important finding demonstrated an age-related retreat from PFC hemispheric asymmetry was not limited to recall tasks but extended to other episodic tasks as well. This reduction in hemispheric asymmetry was interpreted to be a compensatory mechanism to counteract neurocognitive deficits—older adults recruit two hemispheres for a task that requires only one in younger adults (Cabeza Grady 1997, Cabeza 2002). An age-related reduction in asymmetry of PFC activity is observed in other cognitive skills including semantic memory retrieval (Stebbins, Garrillo, Dorfman, Dirksen, Desmond, Turner & Bagrieli, 2002), working memory (Reuter-Lorentz, Jonides, Hartley, Miller, Marshuetz & Koeppel, 2000; Dixit, Gerton, Dohn, et al., 2000), visual

perception (i.e., face matching; Grady, Maisog, Horwitz, Ungerleider, Mentis Salerno & Haxby, 1994) and inhibitory control (Garavan, Ross & Stein, 1999).

The assumption that the left hemisphere is specialized for language does not necessarily hold true across the lifespan with older AWNS demonstrating greater right hemisphere activity than younger AWNS. The inverse may be true for CWNS with younger CWNS demonstrating greater right hemisphere activity than older CWNS. Therefore, the development of atypical cortical activity associated with stuttering requires careful consideration of participants' age.

Neurophysiology of Stuttering.

The neurophysiology of stuttering has been of interest to stuttering researchers since the middle of the 20th century. Researchers have attempted to explain stuttering as a consequence of atypical brain activity since Travis (1931) first described the Cerebral Dominance theory of stuttering that implicated a failure to establish hemispheric dominance within the brain. The following section describes the neurophysiology of stuttering literature from earliest to most recent.

Electroencephalography.

The earliest attempts to examine differences in cortical activity used electroencephalography (Fox, 1966; Freestone, 1942; Helm, et al., 1978; Pinsky et al., 1980). However, artifact due to movement and muscle activity often interferes with EEG recordings, as such the vast majority of EEG studies have focused on differences in linguistic processing. However, advances in data processing has resulted in sophisticated ways to manage different sources of artifact, including artifact related to speech production (Tran, Craig, Boord, & Craig, 2004). Despite this there remain few investigations examining differences between AWS and AWNS

during speech production using EEG. Earlier reports indicate that during speech production tasks AWS show greater amplitude of EEG over the right hemisphere relative to AWNS. This was observed in sentence repetition (Wells & Moore, 1990), a vocabulary test (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983). These early studies were the first to report evidence of atypical laterality during speech production in AWS, a fact that is now well documented by fMRI research.

Positron Emission Tomography (PET).

Examination of functional brain activity during speech production is a valuable tool for describing differences in brain activity that emerge between stuttering and normally fluent populations. The earliest attempts to measure functional brain activity utilized PET to describe differences in functional brain activity between AWS and AWNS. Among the first reports of atypical brain activity during speech production is the report by Fox et al., (1996) that reported AWS demonstrated atypical laterality of speech production characterized by increased right hemisphere activity in the inferior frontal gyrus, precentral gyrus and superior temporal gyrus. The group also reported decreased activity in left hemisphere regions including the precentral gyrus, inferior frontal gyrus and superior temporal gyrus.

Later reports went on to examine changes in cortical activity in AWS during choral speech (Fox et al., 1996), delayed auditory feedback (Foundas, Bollish, Feldman, Corey, Hurley, Lemen & Heilman, 2004), changes in regional blood flow (Ingham et al., 1996), differences in silent versus oral word reading (DeNil et al., 2000), and changes in brain activity in response to short-term and long-term

stuttering intervention (DeNil et al., 2004). In summary, reports from PET were the first to document increased right hemisphere activity in the right inferior frontal gyrus and superior temporal gyrus, decreased activity in the left inferior frontal gyrus, superior temporal gyrus and precentral gyrus. Reports from PET were also among the first to document that choral speech and stuttering intervention resulted in a decrease in the differences in cortical activity between AWS and AWNS.

Functional Magnetic Resonance Imaging.

Over the last 20 years, advances in scientific techniques and technologies have dramatically improved the means by which brain activity can be measured. The utilization of functional magnetic resonance imaging (fMRI) provides a very detailed view of brain activity. fMRI utilizes differences in the magnetic properties of tissues in the brain to determine both structure and function. The differences in the magnetic structure of oxygenated and deoxygenated hemoglobin allow fMRI to depict changes in the concentration of deoxygenated hemoglobin (Raichle, 1998). These changes in oxygen concentration reflect the biological response to metabolic demands of neural tissue. Since the end of the 20th century fMRI has been used to describe both brain structure and brain function in both typical and clinical populations, including stuttering.

There are two findings that are robustly observed in the vast majority of studies: (1) AWS demonstrate increased activity across many regions across the entire brain (Chang, et al., 2009; De Nil, et al., 2008; De Nil, Kroll, & Houle, 2001; Fox, 1996; Ingham, et al., 2003), and (2) AWS demonstrate a substantial increase in activity in right hemisphere homologues of brain regions associated with language

typically lateralized to the left hemisphere (Chang et al., 2009; De Nil, Kroll, Lafaille, & Houle, 2003; Fox, 1996; Fox et al., 2000; Ingham et al., 2004; Neumann et al., 2003, 2005; Preibisch, Neumann, et al., 2003). These regions of increased activity in the right hemisphere are comprised of the homologues of regions typically responsible for generating the motor control for speech production and include the inferior frontal gyrus, SMA, precentral gyrus (particularly the region associated with oro-facial motor activity), anterior cingulate cortex, insula, superior temporal gyrus, the caudate, thalamus, the left cerebellar culmen.

Increased whole-brain activity and decreased laterality of speech production generally co-occur—and have in all reported studies with the exception of one (De Nil et al., 2008), however, they conclude that the failure to observe overactivations in the right hemisphere is likely related to between-group differences in cognitive processes of speech production including automaticity, effort and attention. These authors rightly draw attention to the fact that between-group differences in functional brain activity may not reflect primary dysfunction in speech-motor control, but rather differences in more ancillary features of speech production. These features—particularly effort and attention—may be adaptive responses to experience with stuttering. As such, there is a need for functional brain activity from individuals with limited experience with stuttering—children near the onset of stuttering.

The conclusions from these findings suggest that the cortical control of speech production in AWS requires a greater degree of cortical activity across the brain and specifically in the right hemisphere. It may be suggested that right

hemisphere homologues are compensating for the left hemisphere given that AWS show decreased gray matter volume and relatively disorganized white matter structure underlying the inferior frontal regions (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Foundas et al., 2003). This hypothesis is further supported by increased volume of the corpus callosum in AWS and CWS (Choo, et al., 2011; Choo, et al., 2012). Despite the robust evidence suggesting that AWS use disparate cortical mechanisms for generating speech production, there is limited imaging research parsing the planning of speech movements from their execution.

Neural Correlates of Speech Motor Planning and Execution.

Technological advances have dramatically increased the ability to measure the brain, a fundamental problem to studying speech production remains: the neural signature of speech production will include both the planning and execution of speech production. Dissociating speech motor planning from execution by imaging procedures requires a careful selection of contrast conditions. The best contrast for a particular neurological function is one that generates the some type of activity (e.g., spatial and temporal resolution and intensity) generated by the experimental condition that is not germane to the neurological function. Thus, when the contrast condition is subtracted from the experimental condition, the only functional activity remaining is that of the specific neurological function in question. The earlier studies of functional brain activity in AWS did not use contrasts capable of dissociating planning from execution, thus the results these experiments convey is that of mixed motor planning and execution. Thus, it is impossible to ascertain

whether the disorder of stuttering is manifest by error in motor planning, execution or both.

Two imaging studies have successfully dissociated motor planning and execution. One group acquired two fMRI scans during every stimulus—participants were instructed to repeat a word, syllable or non-speech oral behavior (e.g., cough). The participants produced the stimulus after a go signal. One fMRI scan was gathered before production and the second after production (Chang et al., 2009). This study found that AWS demonstrated evidence of atypical speech-motor planning characterized by deactivations in brain activity relative to AWNS in both cortical and subcortical regions. Cortical regions included the precentral gyrus, bilaterally, the right inferior parietal lobule and the left cingulate gyrus. During speech-motor execution, however, the results revealed AWS demonstrated atypical activity characterized by both deactivations and overactivations of cortical and subcortical regions. Areas of deactivation were primarily located in the left hemisphere and included the precentral gyrus bilaterally, right cingulate gyrus, left superior and middle temporal gyri, left inferior parietal lobule and supramarginal gyrus. Areas of overactivation were located in both the left and right hemispheres and included the right inferior frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, the left supplementary motor area, cingulate gyrus, and bilaterally in the precentral gyrus and Heschl's Gyrus. These results suggest that speech-motor planning in AWS is characterized by decreased activity in the left hemisphere relative to AWNS. Speech-motor execution in AWS, however, is characterized by regions of both increased and decreased activity with right

hemisphere regions potentially compensating for reduced activity in their homologous regions in the left hemisphere.

A second group used one-syllable words, three syllable words and thrice repeated one syllable words to contrast motor planning and motor execution. Regions pertaining to motor planning and motor execution were identified with a significant interaction between planning and execution. Between-group differences then identified regions of atypical neural substrates of motor planning and execution (Lu, Chen, et al., 2010). In contrast to Chang, et al., (2009) evidence of atypical speech-motor planning among AWS could be characterized by evidence of both deactivations and overactivations compared to AWNS. Areas demonstrating deactivations included the left superior temporal gyrus, angular gyrus, and the right medial frontal gyrus. Areas demonstrating overactivations included the right superior temporal gyrus, right post central gyrus, and bilaterally in the inferior, middle and superior frontal gyri. Similarly, during speech-motor execution, regions of atypical activity include areas within both hemispheres that can be characterized by either deactivation or overactivation relative to AWNS. The only cortical region demonstrating deactivations was the left middle temporal gyrus. Cortical regions demonstrating overactivations were observed bilaterally in the inferior, medial and middle frontal gyri, the right superior frontal gyrus, superior temporal gyrus, and the left post central gyrus. These results are largely consistent with previous literature with notable exceptions, in contrast to Chang et al., (2009) atypical substrates of speech-motor planning were observed in both hemispheres and included areas of deactivations and overactivations. This may be due to the fact that

the Lu, Chen, et al., (2010) study obtained measures of speech-motor planning while speech was ongoing, whereas Chang (2009) measured speech-motor planning prior to speech production.

Taken together these studies suggest that, relative to the speech of AWNS, the speech of AWS is under planned and over produced. During speech-motor planning regions of overactivation are spread throughout the brain, however, the regions in the right hemisphere often align with homologous regions in the left hemisphere. One region that has received substantial attention is the right inferior frontal gyrus. The frequent reports of overactivation in this region are thought to be compensatory for planning deficits in the left inferior frontal gyrus (Preibisch, Neumann, et al., 2003, Lu, Chen et al., 2010). During speech-motor execution brain activity was spread throughout the brain and in regions associated with monitoring of speech production (e.g., superior temporal gyrus). Similarly, subcortical neural networks have been implicated to contribute to atypical speech motor execution, particularly the cerebellum (DeNil, et al., 2001; Fox, et al., 2000) and the basal ganglia (Civier, Bullock, Max, & Guenther. 2013; Lu, Peng, 2010). These are the only two studies to date that have attempted to parse speech-motor planning and execution. Consensus has yet to be achieved on the neural substrates of atypical speech-motor planning and execution. Further, these results are only applicable to AWS and have no ability to inform on the onset and development of stuttering. The question of whether CWS demonstrate atypical speech motor planning, motor execution or both continues to be an open question.

Functional Near-Infrared Spectroscopy (fNIRS)

Despite the paucity of functional imaging data from CWS there is a rich literature of functional imaging across a variety of tasks, including language processing, from preschool-aged and school-aged CWNS (Ahmad, Balsamo, Sachs, Xu, & Gaillard, 2003; Holland et al., 2001; Plante, Schmithorst, Holland, & Byars, 2006; Wilke et al., 2006). Thus, it is possible to obtain fMRI data from children. However, it appears that CWS do not tolerate imaging procedures as well as CWNS. In ongoing, structural imaging work at Michigan State University and the University of Michigan the researchers there reported that a higher proportion of data from CWS are unusable due to unsatisfactory amounts of motion artifact (Chang, personal communication, 2014). This may be related to differences in temperament between PCWS and PCWNS. As a group PCWS demonstrate reduced inhibitory control (Eggers et al., 2013) potentially contributing to the increased movement in the scanner relative to CWNS. This data loss may result in a biased dataset. There remains a substantial need for a non-invasive method of obtaining functional imaging data that is more appropriate for measuring functional brain activity in CWS. One technology with great potential is functional Near-Infrared Spectroscopy (fNIRS).

Functional MRI measures subtle differences in the magnetic properties of oxygenated (HbO) and deoxygenated (HbR) hemoglobin (Raichle, 1998). Immediately following activity there is a predictable change in the concentration of oxygenated hemoglobin. Brain regions that have generated action potentials must take up oxygen from the blood stream to replenish metabolic deficits.

Simultaneously there is an increase in overall blood flow to these regions. This results in a pattern of cerebral blood flow that is characterized by an increase in oxygenated hemoglobin and a decrease in deoxygenated hemoglobin (Ferrari & Quaresima 2012). This index of brain activity is called the Hemodynamic Response Function (HRF). fNIRS uses photons at specific wavelengths to measure the HRF by penetrating the surface of the skull and reflected off tissues in the brain. The reflected photons are then detected at the surface of the scalp

NIRS uses two wavelengths of light (690nm and 830nm) to measure the relative proportions of HbO and HbR in brain tissue. These two wavelengths are critical to the function of fNIRS because of a differential response between HbO and HbR in the absorption of photons with wavelengths near the infrared range. This differential in photon absorption is why oxygenated blood appears bright red and deoxygenated blood appears to be a deeper red. During acquisition of fNIRS data, an array of light sources and light detectors are placed directly on the scalp. These optodes are contained in a housing structure that keeps them affixed to the head in a stationary position relative to the head. This housing structure is typically an electroencephalography cap or a strap with a hook and loop closure (Velcro) that wraps around the head.

When light enters the head from light sources it continues on a random path through the head. As such, some photons will pass through scalp, sub dermal tissue, cranial bone, and meninges to enter brain tissue and will subsequently wander out again whereby they can be detected by light detectors. This process has been simulated using Monte Carlo simulations of photon paths through the head (Boas et

al., 2002). We can be reasonably sure that photons detected by light detectors entered brain tissue by placing detectors approximately three centimeters apart from light sources. When measuring the differential response in the two wavelengths of light emitted from light sources, three optical properties of the HRF can be observed: 1) an absolute increase in total blood flow 2) a relative increase in HbO and 3) a relative decrease in HbR (for a full review of fNIRS recordings of the HRF the reader is referred to the following publications: Ferrari & Quaresima, 2012; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993).

Advantages of fNIRS compared to fMRI.

NIRS has several advantages relative to fMRI. fNIRS is substantially less expensive than fMRI, this is not only true of the initial investment but also in terms of operating costs. Unlike fMRI, fNIRS is portable—it can easily be moved within and between buildings. fNIRS is less susceptible to motion artifact than fMRI: the optodes move with the head. However, most crucially for the present study is the fact that fNIRS is far less invasive than fMRI. The data acquisition procedures of fNIRS are remarkably similar to that of electroencephalography—fNIRS requires donning a cap or other optode housing structure and minimal adjustments to optode placement for acquisition of good signals rather than immobilization in a confined place that is typical of fMRI. fNIRS does have functional limitations that must be accounted for. fNIRS is capable of obtaining the HRF from the outer most cortical regions only. It is not possible to gather the HRF from deep cortex (e.g., insula, cingulate gyrus) or subcortical regions using fNIRS. Additionally, the spatial resolution of fNIRS is markedly reduced compared to fMRI. Rather than a 9mm^3

voxel resolution, the source-detector distance defines the spatial resolution of fNIRS (thus, in many studies the spatial resolution is 3cm). For many researchers these limitations are an easy sacrifice to make given the functional benefits of fNIRS, particularly with the gains in participation population.

Tasks across a wide spectrum are routinely used to gather the HRF via fNIRS from infants (Bortfeld, Wruck, & Boas, 2007), children (Buss, Fox, Boas, & Spencer, 2013) and adults (Holper, Biallas, & Wolf, 2009). Many tasks used to generate the HRF are ones that can be used in fMRI—indeed much of the early work in fNIRS was validation that the HRF obtained from fNIRS is functionally equivalent to the HRF obtained from fMRI (Ferrari & Quaresima, 2012; Villringer et al., 1993). However, the flexibility of fNIRS allows data acquisition during tasks fMRI is incapable of measuring including the HRF during conversation (Suda, Takei, Ayoama, Narita, Sakurai, Fukuda, Mikumi, 2011; Suda, Takei, Ayoama, Narita, Sato, Fukuda, Mikumi, 2010).

Optode Position.

It is critical to any study of brain activity to identify the location of brain activity. During fMRI, the location of brain activity can be plotted in relative position to the size of the brain on standardized brain atlases. fNIRS, however, lacks this capability because brain activity is plotted relative to the scalp and not relative to the three dimensional shape of the brain. Thus, determining optimal optode location can be a difficult and arduous process. Until very recently, fNIRS studies used an array of optodes and detectors with a standard 3cm source-detector distance. The array was plotted in reference to the 10-20 scalp coordinate system. This allows a

reasonable degree of certainty that an optode array placed on a scalp coordinate over a region of cortex known to be responsible for a particular neural function will record the HRF related to that neural function. That is, an optode array placed over T7 will record the HRF close to auditory association areas in the left hemisphere, helpful for evaluating receptive language processing (Bortfeld et al., 2007).

Other groups used structural MRI scans to determine optimal array placement (Sato et al., 2011). Requiring a structural brain scan of each subject drastically reduces the cost effectiveness of fNIRS, as such, this is not a reasonable strategy for determining optode placement. Aside from the increased expense, these static strategies for determining optode placement do not allow for a dynamic analysis of a goodness of fit of the optode array over the regions of interest (ROI). A new strategy being developed at the University of Iowa allows a custom optode array and a dynamic analysis of the goodness of fit for that optode array over the ROIs (Wijeakumar, Spencer, Bohache, Boas & Magnotta, 2015). This strategy obtains ROIs from the seminal literature, plots modeled optode placement and runs Monte Carlo simulations. The Monte Carlo simulations of the optode array are then plotted together with identified ROIs in standardized brain space to determine the array's goodness of fit. This process culminates in a series of caps of different circumferences with an optode array that is scaled to the size of the cap and capable of obtaining cortical activity from the ROIs identified. This is advantageous because it allows the optodes to be placed on the scalp at similar locations with relative positions that are consistent across individuals with different head circumferences (e.g., ages).

Statement of the Problem

Speech production is the combined result of speech-motor planning and execution. Stuttering is the developmental disorder of speech production resulting in interruptions in the timing of speech-motor events. AWS demonstrate atypical brain activity during both the planning and execution of speech-motor events, notably evidenced by increased right hemisphere activity of regions of the brain associated with speech-motor control. It remains unclear whether these broad group differences in cortical activity reflect a cause or a consequence of stuttering. Deeper still, it is not clear whether the atypical movements associated with stuttering are the result of atypical speech-motor planning execution or both.

Additionally, the vast majority of data regarding stuttering comes from AWS. This disallows any discussion of the development of stuttering as differences between AWS and AWNS may not be related to stuttering itself, but adaptive reactions to a lifetime of stuttering. This is particularly true of investigations into functional brain activity related to stuttering. It is not possible to distinguish primary affects of stuttering from neural reorganization as a result of experience with stuttering. Nevertheless, the conclusions from functional imaging studies often report that differences between AWS and AWNS reflect risk factors for the development of stuttering. This is an inappropriate conclusion. Differences between AWS and AWNS can only reflect differences between fully developed fluent and disfluent speakers. As such, CWS and age-matched peers are the optimal population to study the development of stuttering.

Chapter 3: Methods

Participants

A total of 45 subjects participated in this study. In total 30 adults participated (15 AWS, 15 AWNS) and 15 children (seven CWS, eight CWNS). Adult and child participants were recruited through the University of Iowa community. A majority of CWS (five of seven) were recruited through a weeklong residential summer camp for children and teens who stutter at the University of Iowa. In order to be included in analysis participants had to be right-handed, monolingual speakers of English. Additionally, participants were required to have negative histories of speech and/or language disorders (other than stuttering), neurological disorders and currently not taking medications for the treatment of attention deficit disorder.

Adult participants and the parents of child participants completed a communication history questionnaire. In order to be considered, stuttering participants had to achieve at least two of the following: (1) be rated greater than 1 on a 0-7 severity rating scale by a clinician highly skilled in the area of stuttering, (2) described their speech as containing stuttering-like disfluencies (as defined by Yairi, 1997) in the communication history questionnaire, (3) received a diagnosis of stuttering from an ASHA certified speech-language pathologist and (4) demonstrate self (adult) or parental (child) concern regarding stuttering. Please see Tables 1 and

2 for selected subject responses from the Communication History Questionnaire. Both of the Communication History Questionnaires can be found in Appendix A. All procedures were completed according to guidelines of the University of Iowa Institutional Review Board on Human Subjects.

Adult Participants

All 30 adults were included in the fNIRS analysis. AWS were not distinguishable from AWNS in terms of age or education. Mean age of AWS was 27.1 (8.15) years, and the average age for AWNS was 26.01(3.45) years ($p = 0.21$). On average, AWS completed slightly less than a bachelors degree (15.1[3.59] years), while AWNS completed a bachelors degree (16.4 [2.28] years). (see Table 3).

Stuttering severity was judged the participant and a speech pathologist experienced in evaluating stuttering. Both severity scales were comprised of an eight point scale where 0 indicated no stuttering and 7 indicated very severe stuttering. On average the participants self rated their own severity as 3.5 (SD = 1.1) the Clinician rating scales averaged 3.7 (SD = 1.1). Results from the Communication History Questionnaire endorsed AWS self-perception that they produced at least two stuttering-like disfluency (SLD) types, as defined by Yairi (1997 (see Table 4).

AWSs' report of stuttering onset averaged 4.7 (1.68) years (range 3-7 years), and is within epidemiological expectations as defined by incidence and prevalence studies of the late 1990s and into the 21st century (Masson, 2010; Yairi & Ambrose 1992a; 1992b).

Child Participants

Twelve of the 15 subjects were included in the fNIRS analysis. One CWS and one CWNS were excluded from analysis because they were left-handed, and a second CWNS was excluded because of issues related to data quality. On the whole CWS were indistinguishable from CWNS in terms of age and parents' education. On average CWS were 11.8(1.27) years and CWNS were 11.2(1.27) years ($p = 0.495$). On average the parents of CWS had completed more than a bachelors degree (17.71[2.43]years). The parents of CWNS had earned a similar degree of education (16.5[3.94]years). Please see Tables 5 and 6 for a breakdown of descriptive statistics.

All parents of CWS rated their child's stuttering severity significantly greater than parents of CWNS. All CWS produced at least two types of within word disfluencies. The parent of only one CWNS indicated the presence of single syllable whole word repetitions and part-word repetitions. This parent indicated no concern regarding stuttering.

| Subject ID | Group | Education (Degree Completed) | Age (years) | Gender | Age of Onset (years) | Part word repetitions | Single Syllable Whole Word Repetitions | Prolongations | Silent Prolongations | Muscle Tension | Frequency Self Rating | Severity Self Rating | Clinician Severity Rating | Family History of Stuttering |
|------------|-------|---------------------------------|-------------|--------|----------------------|-----------------------|--|---------------|----------------------|----------------|-----------------------|----------------------|---------------------------|------------------------------|
| 1201 | AWS | 12 | 19 | M | 5 | yes | yes | no | yes | yes | Freq. | 4 | 4 | no |
| 1202 | AWS | 18 | 28 | M | 5 | yes | yes | yes | yes | yes | Freq. | 3 | 5 | yes |
| 1203 | AWS | 18 | 32 | M | 3 | yes | no | no | yes | yes | Some. | 3 | 5 | yes |
| 1204 | AWS | 16 | 31 | M | 8 | yes | yes | no | yes | yes | Freq. | 4 | 5 | yes |
| 1205 | AWS | 12 | 20 | F | 5 | yes | yes | no | yes | -- | Some. | 3 | 3 | no |
| 1206 | AWS | 12 | 23 | M | 5 | no | yes | no | yes | yes | Some. | 2 | 4 | no |
| 1207 | AWS | 20 | 43 | M | 3 | yes | yes | yes | yes | no | Freq. | 5 | 2 | yes |
| 1208 | AWS | 20 | 38 | M | 4 | yes | no | yes | yes | yes | Freq. | 5 | 5 | yes |
| 1209 | AWS | 20 | 37 | M | 5 | yes | yes | no | no | no | Some. | 2 | 4 | no |
| 1210 | AWS | 18 | 27 | F | 4 | yes | no | no | yes | no | Some. | 2 | 4 | no |
| 1211 | AWS | 12 | 18 | M | -- | no | no | no | yes | yes | Some. | 3 | 2 | yes |
| 1212 | AWS | 12 | 32 | F | 5 | yes | no | yes | yes | yes | Freq. | 4 | 2 | no |
| 1213 | AWS | 12 | 19 | M | 3 | yes | no | yes | yes | yes | Freq. | 5 | 4 | yes |
| 1214 | AWS | 12 | 20 | M | 8 | -- | yes | -- | yes | yes | Some. | 3 | 4 | no |
| 1215 | AWS | 12 | 19 | F | 3 | yes | yes | yes | yes | yes | Freq. | 4 | 3 | no |
| 1101 | AWNS | 18 | 24 | F | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1102 | AWNS | 18 | 30 | F | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1103 | AWNS | 18 | 28 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1104 | AWNS | 18 | 26 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1105 | AWNS | 16 | 30 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1106 | AWNS | 18 | 29 | F | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1107 | AWNS | 16 | 23 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1108 | AWNS | 16 | 23 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1109 | AWNS | 16 | 23 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |
| 1110 | AWNS | 16 | 26 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 1111 | AWNS | 12 | 22 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 1112 | AWNS | 18 | 31 | M | -- | -- | -- | -- | -- | -- | Never | 0 | 0 | no |
| 1113 | AWNS | 12 | 22 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 1114 | AWNS | 18 | 31 | M | -- | -- | -- | -- | -- | -- | Never | 0 | 0 | no |
| 1115 | AWNS | 16 | 23 | M | -- | -- | -- | -- | -- | -- | -- | -- | 0 | -- |

Table 1. Selected Subject Responses from Communication History Questionnaire: Adults.

A selection of responses from the Communication History questionnaire. Education (Degree Completed) 12 = high school, 16 = bachelors degree, 18 = masters degree, 20 = doctorate degree. Part word repetitions, single syllable whole word repetitions, prolongations, silent prolongations are considered stuttering like disfluencies as defined by Yairi (1997).

| Subject ID | Group | Parent's Highest Level Education (Degree Completed) | Age | Gender | Age at Stuttering Onset | Part Word Repetitions | Single Syllable Whole Word repetitions | Prolongations | Silent Prolongations | Muscle Tension | Parent Frequency Rating | Parent Severity Rating | Clinician Severity Rating | Family History of Stuttering |
|---|-------|---|--------|--------|-------------------------|-----------------------|--|---------------|----------------------|----------------|-------------------------|------------------------|---------------------------|------------------------------|
| 2201 | CWS | 18 | 10;11 | M | 3 | yes | yes | yes | no | no | Some. | 3 | 3 | no |
| 2202 | CWS | 14 | 9;6 | F | 7 | yes | no | yes | no | no | Freq. | 3 | 3 | yes |
| 2203* | CWS | 20 | 12;8 | M | 3 | no | yes | yes | yes | yes | Freq. | 7 | 6 | yes |
| 2204 | CWS | 16 | 12;10 | F | 3 | yes | -- | -- | -- | yes | Rarely | 3 | 3 | no |
| 2205 | CWS | 20 | 12;11 | M | 6 | yes | no | -- | yes | no | Some. | 2 | 4 | -- |
| 2206 | CWS | 16 | 12;6 | F | -- | -- | -- | -- | -- | -- | -- | -- | 4 | -- |
| 2207 | CWS | 20 | 11;5 | M | 4 | yes | no | yes | yes | -- | Some. | 4 | 4 | yes |
| 2101 | CWNS | 20 | 9;7 | F | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| 2102 | CWNS | 12 | 11;1 | F | -- | no | no | no | no | no | Never | 0 | 0 | yes |
| 2103 | CWNS | 12 | 9;7 | M | -- | yes | yes | no | no | no | Some. | 1 | 0 | yes |
| 2104 | CWNS | 20 | 10; 11 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 2105* | CWNS | 20 | 10; 11 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 2106* | CWNS | 20 | 12;8 | F | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| 2107 | CWNS | 12 | 12;1 | M | -- | no | no | no | no | no | Never | 0 | 0 | no |
| 2108 | CWNS | 16 | 12;8 | F | -- | no | no | no | no | no | Never | 0 | 0 | no |
| * 2203, 2105 and 2106 were not included in the fNIRS analysis. 2203 and 2105 were left handed, the fNIRS recordings from 2106 were of poor quality. | | | | | | | | | | | | | | |

Table 2. Selected Subject Responses from Communication History Questionnaire: Children.

A selection of responses from the Communication History questionnaire. Education (Degree Completed) 12 = high school, 16 = bachelors degree, 18 = masters degree, 20 = doctorate degree. Part word repetitions, single syllable whole word repetitions, prolongations, silent prolongations are considered stuttering like disfluencies as defined by Yairi (1997).

| | AWS | | AWNS | | df | T | p |
|---------------------------------|--------|--------|-------|-------|--------|--------|----------|
| | M | SD | M | SD | | | |
| Education* | 15.07 | 3.588 | 16.4 | 2.284 | 22.318 | 1.27 | 0.2182 |
| Age (years)* | 27.07 | 8.155 | 26.07 | 3.453 | 18.864 | -0.44 | 0.6668 |
| Age of Onset | 4.714 | 1.637 | -- | -- | -- | -- | -- |
| Severity Self Rating NR = 0* | 3.4667 | 1.0601 | 0 | 0 | 14 | -12.67 | < 0.0001 |
| Clinician Severity Rating* | 3.7333 | 1.0998 | 0 | 0 | 14 | -13.15 | < 0.0001 |

* reflects Satterthwaite correction for unequal variances

Table 3. Descriptive Statistics: Adults.

A selection of responses from the Communication History Questionnaire. The Self Severity Rating and Clinician Severity Rating Scales reflect an eight point Likert scale ranging from 0-7 where 0 reflects no stuttering present and 7 reflects extremely severe stuttering. Generally 0-1 is considered normal fluency, 2-3 mild stuttering, 4-5 moderate stuttering and 6-7 severe stuttering.

| | AWS | | AWNS | |
|-----------------------|-----|---------|------|-------|
| | Yes | No / NR | Yes | No/NR |
| Part word repetitions | 12 | 3 | 0 | 15 |
| SSWW repetitions | 9 | 6 | 0 | 15 |
| Prolongations | 6 | 9 | 0 | 15 |
| Silent Prolongations | 14 | 1 | 0 | 15 |
| Muscle Tension | 11 | 4 | 0 | 15 |
| Yes to 5 | 2 | | 0 | |
| Yes to 4 | 6 | | 0 | |
| Yes to 3 | 4 | | 0 | |
| Yes to 2 | 3 | | 0 | |

Table 4. Within-Word Disfluency Characteristics: Adults.

A selection of responses from the Communication history Questionnaire. The specific items come from Yairi (1997) where Part-word repetitions, single syllable whole word repetitions (SSWW), Prolongations and Silent Prolongations reflect stuttering-like disfluencies.

| | | CWS | | CWNS | | df | T | p |
|---------------------------------|---|-------|-------|-------|-------|-------|-------|---------|
| | | M | SD | M | SD | | | |
| All Subjects | Education | 17.71 | 2.43 | 16.5 | 3.941 | 13 | -0.7 | 0.4954 |
| | Age (Months) | 11.82 | 1.27 | 11.23 | 1.27 | 13 | -0.88 | 0.3935 |
| | Age of Onset | | | -- | -- | -- | -- | -- |
| | Parent Severity Rating Early NR = 0* | 2.71 | 2.81 | 0.125 | 0.353 | 6.166 | -2.42 | 0.05 |
| | Parent Severity Rating Now NR = 0* | 3.14 | 2.11 | 0.125 | 0.353 | 6.29 | -3.73 | 0.0089 |
| | Clinician Severity Rating* | 3.85 | 2.86 | 0 | 0 | 6 | -9.55 | <0.0001 |
| | | | | | | | | |
| Only Subjects in fNIRS Analysis | Education | 18 | 2.52 | 15.33 | 3.93 | 10 | -1.4 | 0.1927 |
| | Age (Months) | 11.05 | 1.34 | 11.65 | 1.31 | 10 | -0.78 | 0.4523 |
| | Age of Onset | | | -- | -- | -- | -- | -- |
| | Parent Severity Rating Early NR = 0* | 3.4 | 3.049 | 0.16 | 0.4 | 4.12 | -2.6 | 0.0763 |
| | Parent Severity Rating Now NR = 0* | 3.166 | 2.31 | 1.66 | 0.037 | 5.31 | -3.12 | 0.0108 |
| | Clinician Severity Rating* | 4 | 1.09 | 0 | 0 | 5 | -8.94 | 0.0003 |
| | | | | | | | | |

Table 5. A selection of responses from the Communication History Questionnaire-Child. The Parent Severity Rating and Clinician Severity Rating Scales reflect an eight point Likert scale ranging from 0-7 where 0 reflects no stuttering present and 7 reflects extremely severe stuttering. Generally 0-1 is considered normal fluency, 2-3 mild stuttering, 4-5 moderate stuttering and 6-7 severe stuttering. * reflects Satterhwaite correction for unequal variances

| | CWS | | CWNS | |
|-----------------------|-----|---------|------|-------|
| | Yes | No / NR | Yes | No/NR |
| Part word repetitions | 5 | 2 | 1 | 7 |
| SSWW repetitions | 2 | 5 | 1 | 7 |
| Prolongations | 4 | 3 | 0 | 8 |
| Tense Pauses | 3 | 4 | 0 | 8 |
| Muscle Tension | 2 | 5 | 0 | 8 |
| Yes to 5 | 0 | | 0 | |
| Yes to 4 | 1 | | 0 | |
| Yes to 3 | 2 | | 0 | |
| Yes to 2 | 3 | | 1** | |
| Yes to 1 | 0 | | 0 | |
| Yes to 0 | 1* | | 0 | |

* Reflects a communication questionnaire that was not completed

** Although this parent indicated this subject's speech had some within word disfluencies, the same parent indicated the child's speech fluency was normal and had no concerns regarding stuttering

Table 6. Within-Word Disfluency Characteristics: Child

A selection of responses from the Communication history Questionnaire. The specific items come from Yairi (1997) where Part-word repetitions, single syllable whole word repetitions (SSWW), Prolongations and Silent Prolongations reflect stuttering-like disfluencies.

Tasks and Stimuli

Two tasks were used to isolate cortical activity related to speech-motor planning and execution independently of each other. To isolate cortical activity related to speech-motor execution a covert / overt picture identification task was used. All tokens were of target nouns and selected from the Hatfield Image Test (Adlington, Laws, & Gale., 2009). All tokens were color photographs of the objects presented on a field of white. To be selected for analysis all target nouns had to be acquired before the age of five (cf. the Hatfield Imaging Test). Trial type (e.g., covert v. overt) was distinguished by a color change around the white background of the picture. These two conditions were selected because motor planning processes would be involved in both covert naming and overt naming, however, processes

related to motor execution would be present in the overt naming. As such, what distinguishes these naming tasks is the presence of motor execution.

To isolate cortical activity related to speech-motor planning a nonword repetition task was used. To identify motor planning nonwords had to vary in the degree of motor planning demand but present similar levels of motor execution. Therefore, two different types of nonwords were created that all had three syllables. Each nonword was comprised of three of the same syllables or three different syllables. All nonwords were developed from a selection of the tokens used in the motor execution task. To create nonwords with three identical syllables the phonemes of tokens in the motor execution task with only one syllable were randomized together to create nonsense syllables. However, the syllable position of each phoneme was preserved (e.g., initial phonemes were always initial phonemes). To create nonwords with three different syllables the syllables for tokens with three syllables were randomized to create nonsense words. The position of syllables within the word was preserved (e.g., first syllables were always first syllables). All nonwords have a similar degree of motor execution, as such the two types of nonwords primarily differ in the level of motor planning necessary.

NIRS Cap Construction

The process of cap construction was essential for accurate data collection. This is a multi-step process consisting of region of interest (ROI) selection, optode geometry development and grommet installation. This process is briefly described here, a comprehensive description of the process can be found in Appendix A.

To measure functional brain activity using fNIRS a priori decisions regarding which regions of the cortex to measure were made. To facilitate this process the coordinates of cortical regions describing differences in functional brain activity between AWS and AWNS were obtained from seminal literature. The Euclidian distance between each coordinate and all other coordinates was calculated. All coordinates that clustered within one centimeter were averaged together to obtain the ROIs that would be the bases for the cap design. The process identified seven ROIs in each hemisphere. Each ROI was a sphere with a diameter of one centimeter with the center points the averaged coordinates from the clustered ROIs.

An optode geometry was selected through a process of trial and error. This included identifying potential locations of optodes and validating its effectiveness through simulations of the photon migration paths (Monte Carlo Simulations; Huppert, Diamond, Franceschini & Boas., 2009). The optode geometry's goodness of fit was determined by a visual inspection of the degree of overlap between the ROI spheres and the results of the Monte Carlo Simulations. The final optode geometry consisted of 12 light sources and 24 light detectors combined to form 40 source – detector pairs.

The Monte Carlo simulations were completed using AtlasViewer, a component tool of Homer2 (Huppert, et al., 2009). A Polhemus Patriot was used to calculate the Euclidean distance between five head landmarks (two scalp landmarks: nasion and inion; and three locations on the 10-20 scalp coordinate system: CZ, A1, A2) and all optodes. Monte Carlo simulations were ran simulating the random path of one million photons exiting each light source and detected by

each light detector. The Figure 2 presents the ROIs of the right hemisphere in the upper panel and the results of the Monte Carlo simulations in the lower panel.

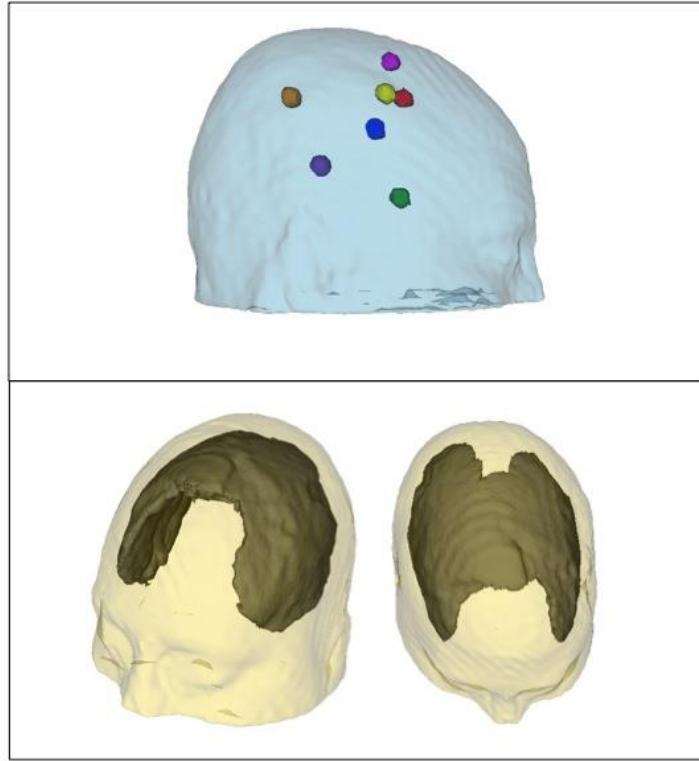


Figure 2. ROIs and Results of Monte Carlo Simulations.

This figure presents the right hemisphere ROIs obtained from seminal fMRI literature in stuttering in the upper panel. The lower panel depicts the results of the Monte Carlo Simulations.

Data Collection

Participants were seated in a chair approximately 24 inches from a television screen. Verbal responses were recorded with a Phillips DV1400/00 digital recorder and a Phillips 9173 lapel microphone. Behavioral responses were recorded using a customized E-Prime program including the output the timing of the stimuli presentation. Correct, incorrect and disfluent responses were indicated by the

researcher's button press. Output from the E-prime software included response accuracy (as indicated by researcher's button press) and the timing of all events (e.g., onset time of stimulus, onset time of response, etc.).

Capping Process.

After participant's consent was obtained the participant's head circumference (passing through the nasion and inion) was measured. An appropriate cap was selected to fit the participant's head. The cap was placed on the head and centered so that the CZ location on the cap was on a line extending from the inion to the nasion at the intersection of a line extending from A1 to A2. After the cap was position correctly it was secured in place with a hook-and-loop strap and optodes were placed into grommets housed within the fabric of the cap.

Each optode had a unique identifier that corresponded to its location in the optode geometry. An unfolded bobby pin was used to expose the scalp within the center of the grommet and the optode was placed against the scalp. After all optodes were in place the light sources were turned on and optical density of each of both wavelengths (690 nm and 830 nm) was observed at each source-detector pair. If optical density was below optimal threshold (90dB) adjustments were made. First, the scalp was confirmed to be free of hair underneath the optodes. If the scalp was free of hair and the optical density was still suboptimal the sensitivity of the optodes was individual adjusted. During the capping process adult subjects conversed with the examiner and research assistant. Child subjects were given the option to view a video on a hand-held DVD player. After good signal quality had been achieved the

Euclidean distance between head landmarks and each optode were obtained using a Polhemus Patriot.

Motor Execution.

A Go/No-Go naming task incorporating both overt and covert naming conditions was used. The participant was naïve to the type of naming condition until the go signal was provided. Exactly 1500ms after the picture appeared the border around the picture changed from black to red or green. If the border changed to red the participant was instructed to name the picture covertly, whereas if the border changed to green the participant was instructed to overtly name the picture. Figure 3 presents the time course of a typical covert trial in the upper panel and overt trial in the lower panel. The participant's response was recorded with a customized E-prime program. Only correct and fluently produced responses were included in the fNIRS analysis.

This task included 42 covert-naming tokens and 42 overt-naming tokens randomized and counter balanced by syllable length into seven blocks each containing twelve tokens. Each participant was presented the blocks in the same order; however, the tokens within the block were individually randomized for each participant. The covert and overt stimuli were primarily the same token, however, there were foils included into the list in order to reduce the predictability of the task. Approximately 25% of the tokens contained foils (11/42 in each covert and overt). Foils were matched for syllable length. In order for overt naming trials to be judged correct participants had to produce the target word exactly or a closely related synonym (e.g., cheeseburger v. hamburger). Responses were recorded using

an a Phillips DV1400/00 digital recorder and a Phillips 9173 lapel microphone.

Another researcher rated the accuracy of 15% of the subjects. Please see appendix C for a list of stimuli. Individual tokens within a block were separated by a jittered inter-trial interval of two, four or six seconds. Following each block participants were allowed a brief rest break the duration of which was up to the participant's discretion.

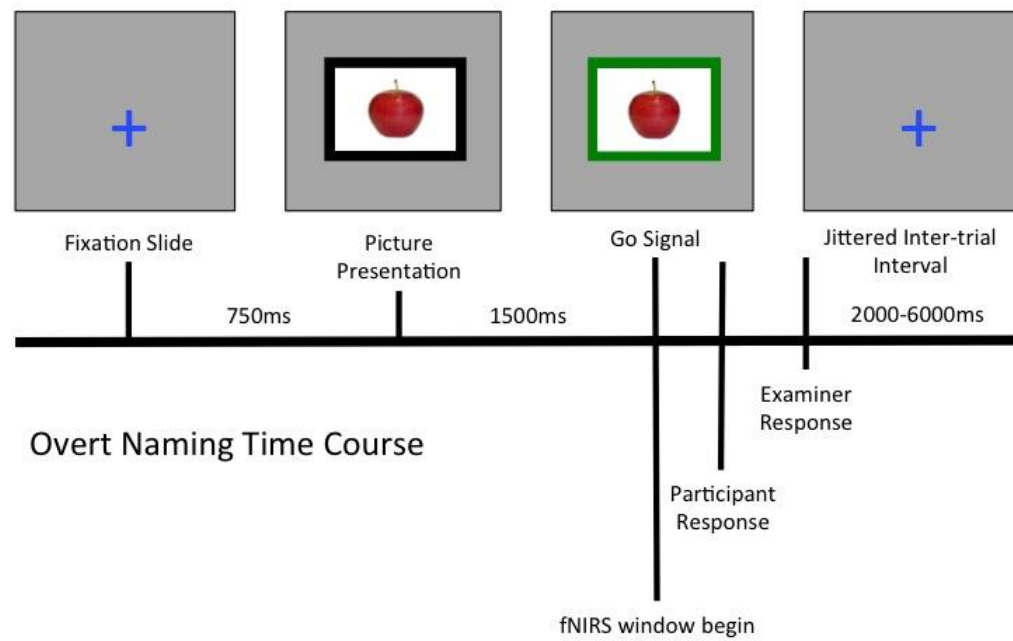
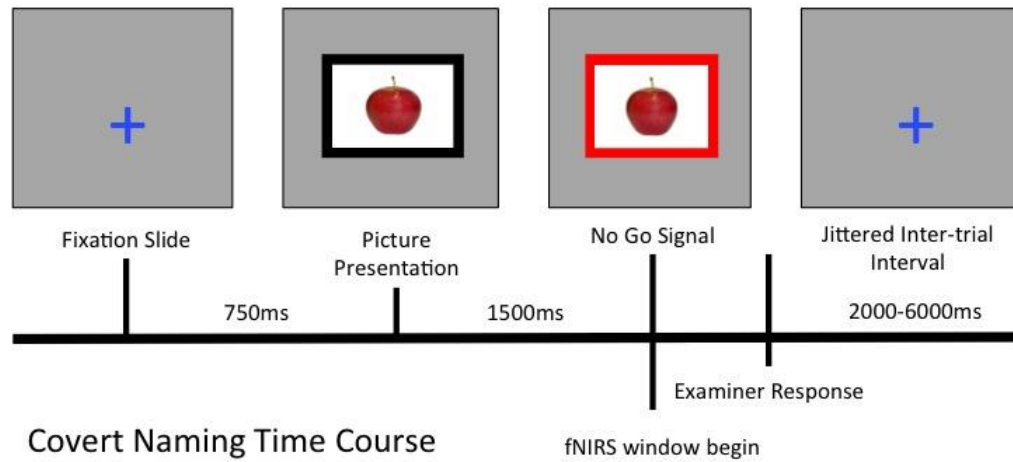


Figure 3. Time Course of the Motor Execution Task.
Covert naming time course in the upper panel, overt naming time course in the lower panel.

Motor Planning.

Following the naming task participants completed a nonword repetition task. In this task the participants heard two types of three-syllable nonwords: nonwords with three different syllables (e.g., “grass-brell-na”) or nonwords with three of the same syllables (e.g., flot-flot-flot). The participants were instructed to repeat the nonword immediately after it was presented. These nonwords were developed from the tokens used in the Picture naming task. The repeated syllable nonwords were developed by randomly distributing the onset, vowel and offset phonemes of one-syllable words included in the picture naming task. The different-syllable nonwords were developed by randomly assigning the first, second and third syllable from the sample of three-syllable words in the picture naming task.

This task included 70 tokens comprised of 35 SSN and 35 DSN. The tokens were comprised of 20 different SSN and 20 different DSN randomized and counter balanced between seven blocks each containing twelve tokens (each nonword was repeated twice and two nonwords were repeated three times). Neither group of nonwords was phonotactically different from each other or the items in the motor execution task ($p < 0.05$). In order to be judged correct participants had to produce the nonwords exactly as it was presented and without disfluencies. Interrater reliability was also completed on the nonword repetition task. Please see Appendix C for a complete listing of stimuli used. Individual tokens within a block were separated by a jittered inter-trial interval of two, four or six seconds. As during the picture naming tasks participants were allowed a brief rest break between blocks.

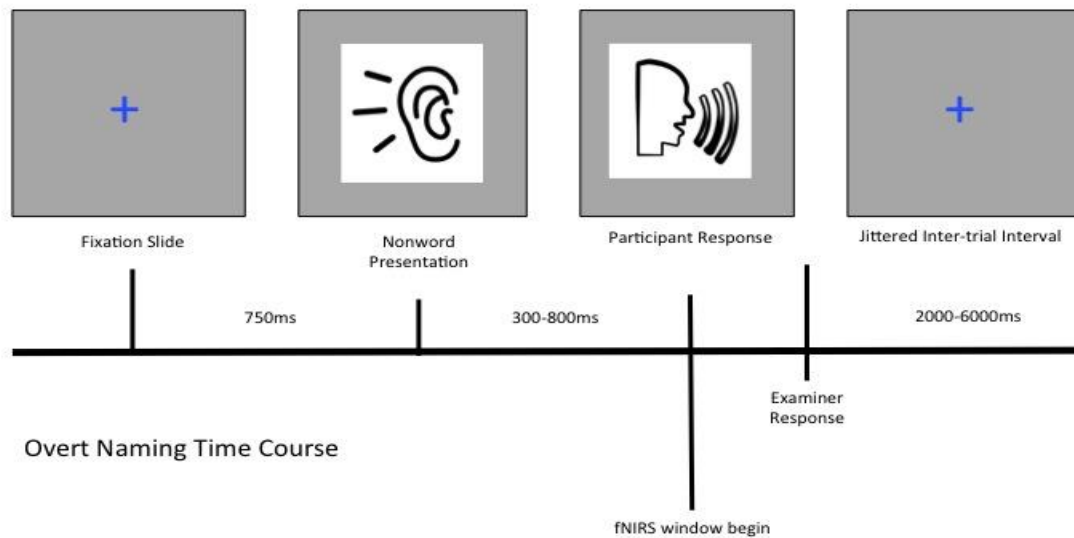


Figure 4. Time course of Motor Planning Task.

Data Analysis

The process of extracting cortical activity requires an extensive process of data analysis. The following section outlines the processing steps to extract the HRF from the fNIRS files.

Within each fNIRS file there are 40 source-detector pair channels. Using targeting principle component analysis channels with motion artifact greater than three standard deviations of average were marked for removal. For each task, a trial

was excluded from analysis if it occurred within one second before or five seconds after an artifact event. The fNIRS files were band pass filtered with a high pass filter of 0.016Hz and low pass filtered at 0.5Hz.

Data from each condition were averaged across a window of 21 seconds. This duration was selected because it captured the rise and fall of the HRF signal, shorter windows concluded before the HRF had returned to baseline. The two tasks utilized two different conventions for assigning the position of the event-related hemodynamic response (HRF) window. For the Picture Identification task the HRF window began one second before the go/ no go signal appeared and concluded 20 seconds after the signal. The HRF window for the Nonword Repetition task began one second before the participant initiated the repetition and concluded 20 seconds after the initiation of the nonword repetition. To identify the time speech onset began, a custom Matlab function was written that first displayed the sound pressure wave then played the sound file in ten second increments. The onset of speech production could then be identified with a mouse click. The time identified by the mouse click was then rectified with the E-prime and NIRS events through the use of an auditory event that E-prime initiated at the onset of each block.

Finally, estimates of the HRF were extracted from the fNIRS file by completing least squares regression performed with a short-source detector that estimated the artifact related to blood supply to the scalp in the NIRS signal. The NIRS data were regressed with four short source-detectors using the `hmrDeconvHRF_DriftSS` function in HomER2 with a distance of 10mm. Results of the regression are beta values for HbO and HbR at each channel. These beta values

indicate the strength of the relationship between a typical HRF and the observed change in the concentration of HbO or HbR.

In order to construct images of brain activity and complete a voxel analysis, further analysis steps were necessary. One hundred million photon Monte Carlo simulations were completed on the digitized head profiles of each participant. This resulted in a sensitivity profile for photon paths through the heads of each subject. These sensitivity profiles were combined together to generate one union mask of common voxels across all subjects. Only voxels that were common across all subjects were included in the union mask. Different union masks were generated for the adult group and the child group.

A custom MatLab script integrated beta values for each subject with that subject's sensitivity profile resulting in a NIFTI file that could be viewed in the software Analysis of Functional NeuroImages (AFNI; Cox, 1996). Results from the regression were converted from channels on the surface of the scalp into an estimate of the local concentration of each light wavelength (690nm, 830nm) within the brain volume using an image reconstruction technique. This approach used Monte Carlo simulations to estimate how light would travel through brain tissue for each source-detector pair. We then used Tichonov Regularization to invert the forward model and estimate a voxel-wise concentration for HbO and HbR. The result of this procedure is an intersection mask, or the common voxels across all subjects that demonstrated significant change in the concentration of the wavelengths associated with HbO or HbR. This procedure is part of a developing

methodology at the University of East Anglia in Norwich, England (Wijeakumar et al., in preparation).

The remaining analysis steps were completed similarly to traditional group-level fMRI analysis procedures. Repeated measures ANOVA were completed with one within-subjects comparison and two between-subjects comparisons. The within subjects comparison was the task (Motor planning: different v. repeated syllable nonwords; Motor Execution: Covert v. Overt Naming) and the between subjects comparisons were group and the interaction between group and task. After the ANOVA was completed clusters of voxels that were at least 80mm³ (10 contiguous voxels) were identified. These clusters were then subjected to family-wise correction for multiple comparisons.

Chapter 4: Results and Discussion

This chapter is divided into five sections. The first provides an analysis of behavioral performance in each task (1). Each of the subsequent sections present the fNIRS results and follows the same format, first presenting within-subjects results, then moving on to between group differences, and finally presenting results of the interaction between condition and group factors. The interaction effect is the primary test of interest—this test presents between group differences in speech-motor planning/execution. Each section then concludes with a discussion describing the meaningfulness of the primary results. The sections proceed as follows: (2) motor planning task in adults, (3) motor planning task in children, (4) motor execution task in adults and (5) the motor execution task in children.

Behavioral Performance

In both the motor planning and motor execution tasks only correct and fluently produced nonwords were included in NIRS analysis. During covert naming tokens were considered incorrect if the participant initiated a speech act after receiving the no-go signal. All other covert tokens were considered correct and included in the analysis. During overt naming tokens were considered correct if the participant labeled the picture with the exact label as identified by (Adlington, et al., 2009). In rare cases obvious synonyms were included (e.g., turtle/tortoise; hamburger/cheeseburger; couch"/"sofa). Overt tokens were considered incorrect if they were incorrectly labeled. Overt tokens were also excluded from analysis if the

participant's response included more than one word (e.g., "double cheeseburger" or "that's an elephant") or if the participant initiated speech immediately after the token. During the nonword repetition task both conditions received the same inclusionary and exclusionary criteria. Tokens were considered correct if they were produced using the same phoneme sequences. Allophonic variations were considered acceptable. Additionally, tokens were excluded from the analysis if the participant initiated a speech act immediately after repeating the token. Table 7 presents the means and standard deviations for the number of tokens included in each task.

In the motor planning task AWNS and AWS demonstrated similar number of tokens in the repeated syllable nonwords ($F_{1,28} = 0.34$, $p = 0.56$). However, AWS produced marginally fewer different syllable nonwords compared to AWNS ($F_{1,28} = 3.69$, $p = 0.0653$). CWNS and CWS demonstrated similar number of included tokens in the repeated syllable nonwords ($F_{1,10} = 0.01$, $p = 0.91$). Like their adult counterparts CWS produced marginally fewer different syllable nonwords than CWNS ($F_{1,10} = 4.55$, $p = 0.0588$).

In the motor execution task AWNS and AWS demonstrated similar number of tokens in the overt naming condition ($F_{1,29} = 1.17$, $p = 0.28$), the covert naming condition, and the covert naming task ($F_{1,29} = 1.04$, $p = 0.31$). CWNS and CWS demonstrated similar number of tokens in the overt naming ($F_{1,10} = 1.43$, $p = 0.25$), although the covert naming condition appears to be significant ($F_{1,10} = 5$, $p = 0.0493$) this is likely due the fact that the standard deviation of the CWS was 0. It

should be noted that the difference between the different syllable nonwords is due to the presence of stuttering and not erroneous repetitions of nonwords.

| | AWNS | AWS | CWNS | CWS |
|------------------------|-------------|-------------|-------------|-------------|
| Motor Planning | | | | |
| Repeated Syllable | 34.1 (2.43) | 32.7 (8.66) | 33.5 (0.84) | 31.3 (2.42) |
| Different Syllable | 32.8 (2.04) | 28.4 (8.56) | 31.5 (2.8) | 25.1 (9.54) |
| Motor Execution | | | | |
| Covert Naming | 41.5 (1.06) | 40.9 (2.01) | 41.5 (0.55) | 42 (0) |
| Overt Naming | 40.1(2.12) | 37.2 (9.79) | 40.5 (2.07) | 37.7 (5.42) |

Table 7. Behavioral Responses included in fNIRS Analysis.
Behavioral results representing the number of correct and fluently produced tokens included in the fNIRS analysis.

Motor Planning: Adults

The data were analyzed using a two-way, repeated measure ANOVA. Condition (repeated or different syllable nonword) was added as a within group factor whereas group membership was added as a between-groups factor. The purpose of this task was to examine motor planning. All nonwords had a similar level of motor execution (three syllables) but differed in the number of syllables planned (one syllable in SSN and three syllables in DSN).

Within Group Differences.

The ANOVA results identified ten clusters of voxels demonstrating a significant difference between repeated and different syllable nonwords that survived a family wise correction for multiple comparisons. These clusters are presented in Table 8.

Recall that the key feature between the two types of nonwords is the degree of speech-motor planning necessary: the different syllable nonwords required a greater degree of speech-motor planning than the repeated syllable nonwords. The voxel clusters that demonstrated significant difference between the repeated and different syllable nonwords were identified either by an increase or decrease in HbO during the different syllable nonwords (relative to repeated syllable nonwords).

Averaged across groups, increased speech-motor planning demand (different syllable nonwords) was associated with an increase in HbO in the left middle frontal gyrus, left precentral gyrus, and the right post central gyrus. Similarly, increased speech-motor planning demand was associated a decrease in HbO in the left superior temporal gyrus, left post central gyrus, as well as the left superior, middle and inferior frontal gyri.

Figure 5 depicts the location of the clusters. Clusters demonstrating increased HbO with high demand nonwords are identified with a red circle while clusters demonstrating increased HbO in low demand nonwords are identified with a blue circle. Also depicted are two typical bar plots, one demonstrating an increase in HbO in the different relative to repeated syllable nonwords (left panel) and another depicting an increase in HbO to the repeated relative to different syllable nonwords (right panel).

| Region | Hem. | BA | Volume (mm ³) | F _{10, 280} | SEM | Talarach Coordinates (RAI) | | |
|--------------------------------|--------------|-----------|------------------------------|----------------------|---------------|-------------------------------|--------------|-------------|
| | | | | | | x | y | z |
| Superior Temporal Gyrus | Left | 42 | 1088 | 5.2882 | 0.0658 | 63.7 | 24.4 | 11.7 |
| Middle Frontal Gyrus | Left | 6 | 792 | 5.3755 | 0.0929 | 40.6 | 0.2 | 52.3 |
| Post central Gyrus | Left | 3 | 544 | 5.1329 | 0.067 | 23.5 | 31.8 | 69.7 |
| Precentral Gyrus | Left | 4 | 456 | 5.794 | 0.1574 | 55.7 | 17.7 | 34.1 |
| Inferior Frontal Gyrus | Left | 45 | 416 | 5.9341 | 0.1773 | 54 | -38.5 | 5.4 |
| Post central Gyrus | Right | 3 | 224 | 7.3878 | 0.4811 | -62 | 13.2 | 24.1 |
| Superior Frontal Gyrus | Right | 6 | 216 | 5.117 | 0.1367 | -23.2 | -7 | 65.5 |
| Middle Frontal Gyrus | Left | 8 | 168 | 4.6187 | 0.0872 | 45.7 | -18 | 43 |
| Inferior Frontal Gyrus | Left | 44 | 128 | 4.8532 | 0.1198 | 57.8 | -14.6 | 19.7 |
| Post central Gyrus | Right | 43 | 48 | 7.0825 | 0.2013 | -60.8 | 10 | 20 |

Table 8. Results from condition differences between the repeated syllable and different syllable nonwords in the Motor Planning task among AWNS and AWS.

Bolded clusters indicate regions where different syllable nonwords > repeated syllable nonwords.

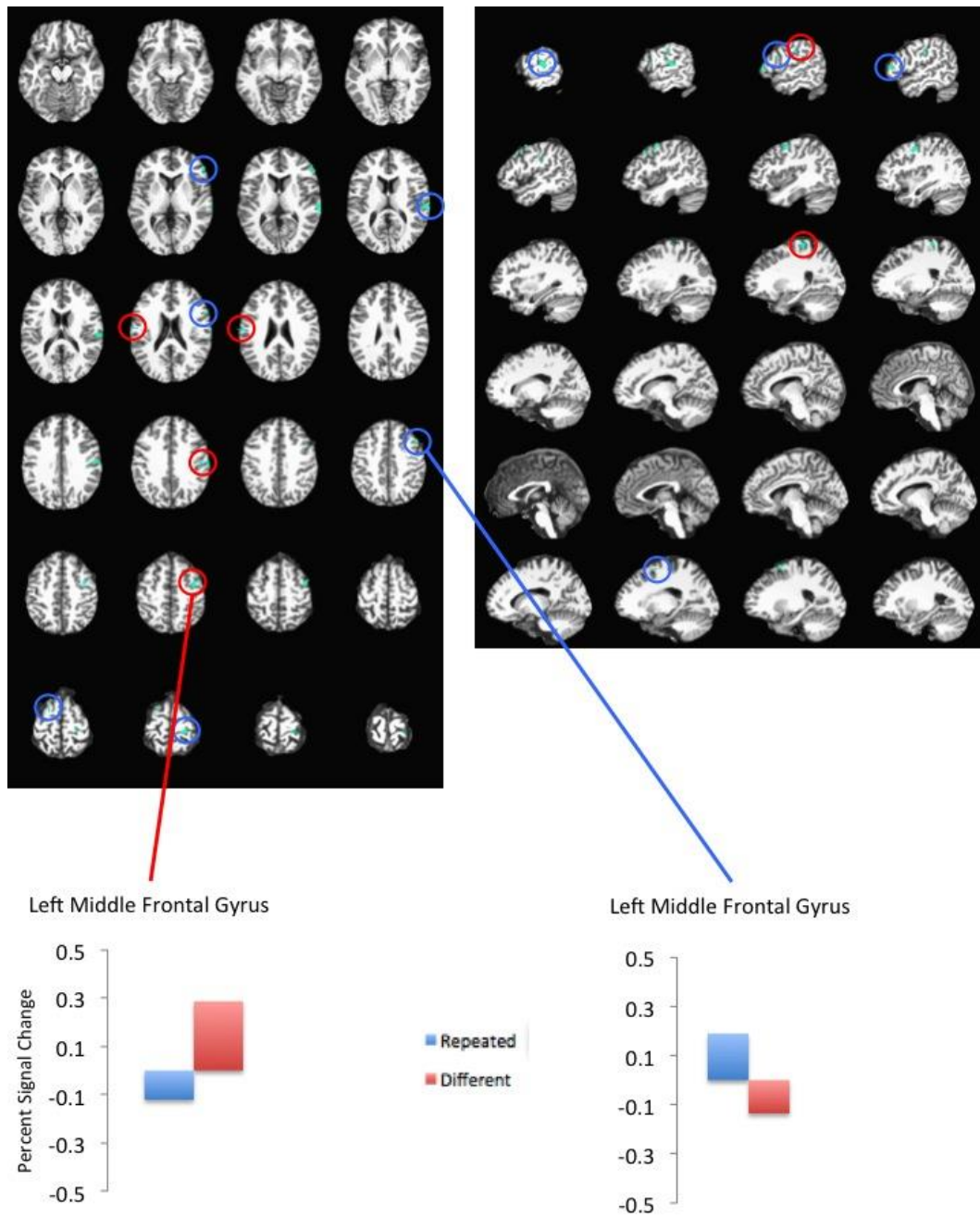


Figure 5. Clusters demonstrating significant condition effect among Adults in Motor Planning. Activity related to repeated syllable nonwords are presented with red circles while activity related to different syllable nonwords is presented with blue circles.

Between Group Differences.

Significant regions in the group comparison reflect clusters where AWS and AWNS demonstrated different levels of HbO averaged across both repeated and different syllable nonwords. These regions do not necessarily reflect atypical speech-motor planning in AWS, but rather indicate regions where AWS demonstrate different levels of activity than AWNS, without accounting for motor planning demand. Results from the ANOVA identified five clusters that survived a family wise correction for multiple comparisons demonstrating a significant difference between the groups. These clusters are presented in Table 9.

The clusters that demonstrated significant difference between AWS and AWNS averaged across repeated and different syllable nonwords. Regardless of speech-motor planning demand AWS demonstrated increased activity than AWNS in the left precentral, left middle frontal and left superior temporal gyrus. Whereas, AWS demonstrated reduced activity relative to AWNS in the left superior frontal gyrus and the right inferior parietal lobule.

Figure 6 depicts the locations of significant voxel clusters that survived the family wise correction for multiple comparisons. Note that clusters where $AWS > AWNS$ are depicted by green circles where as $AWS < AWNS$ are depicted by green squares.

| Region | Hem. | BA | Volume (mm ³) | F _{5, 140} | SEM | Talarach Coordinates (RAI) | | |
|---------------------------------|--------------|-----------|---------------------------|---------------------|---------------|----------------------------|--------------|-------------|
| | | | | | | x | y | z |
| Precentral Gyrus | Left | 6 | 3576 | 5.7653 | 0.0839 | 58.7 | 1.4 | 12.1 |
| Middle Frontal Gyrus | Left | 8 | 1400 | 4.764 | 0.0318 | 37.1 | -19.1 | 48.1 |
| Middle Frontal Gyrus | Left | 6 | 560 | 4.6586 | 0.0374 | 43.2 | 2 | 55.7 |
| Superior Temporal Gyrus | Left | 22 | 144 | 6.0026 | 0.3144 | 66.1 | 30.9 | 9.5 |
| Inferior Parietal Lobule | Right | 40 | 80 | 4.3646 | 0.0405 | -51 | 57.8 | 52.2 |

Table 9. Results from group differences between the repeated syllable and different syllable nonwords in the Motor Planning task among AWNS and AWS.

Bolded clusters indicate regions where AWNS > AWS.

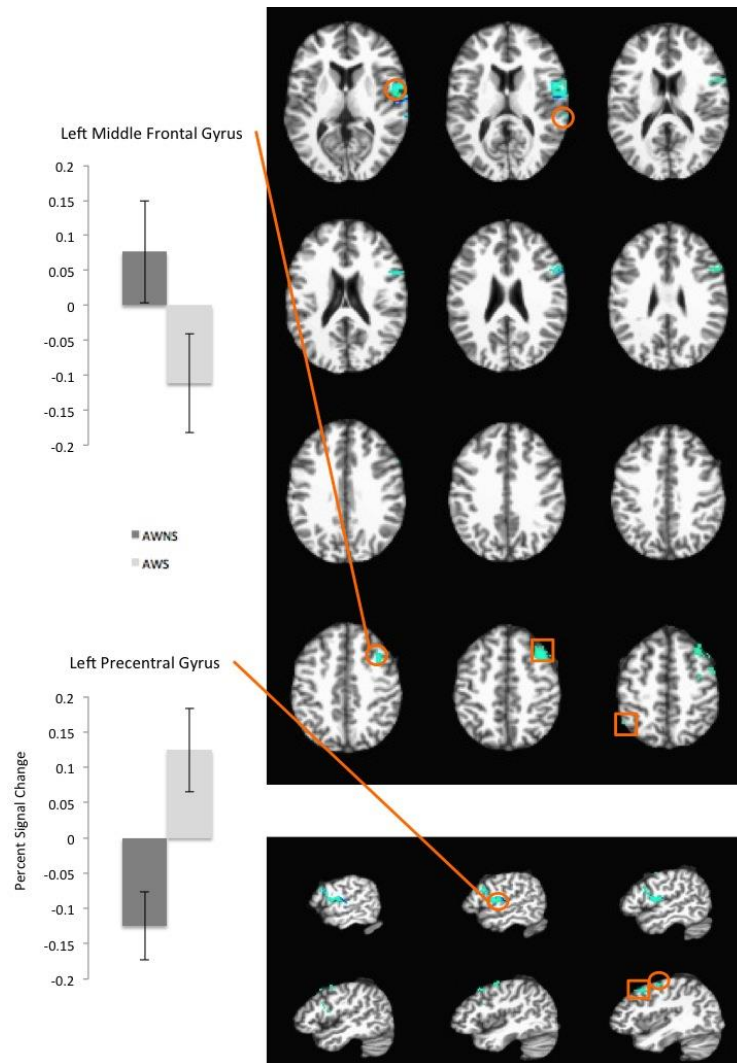


Figure 6. Clusters demonstrating a significant group effect in Motor Planning among Adults. Clusters where AWS > AWNS are depicted with a circle, while clusters where AWS < AWNS are depicted with a square. Dark gray bars reflect activity demonstrated by AWNS whereas light gray depicts activity demonstrated by AWS.

Between-Group Differences in Motor Planning.

The interaction term was used to identify clusters where AWS and AWNS demonstrated different patterns of cortical activity between the conditions. The ANOVA results from the group by condition interaction term reflect regions of atypical speech-motor planning among AWS. Table 10 presents the clusters that survived the correction for multiple comparisons.

Among AWNS, increased speech-motor planning demand was associated with reduced activity in the right inferior frontal gyrus and the right precentral gyrus. However, in those same regions AWS demonstrated an increase in cortical activity. Likewise, among AWNS increased speech-motor planning activity was associated with an increase in cortical activity in the left inferior frontal gyrus, left precentral gyrus, and the right middle frontal gyrus. However, AWS demonstrated a decrease in those same regions.

Post hoc t-tests were completed to determine if AWS and AWNS demonstrated significantly different levels of cortical activity during each condition at each significant cluster. During the repeated syllable nonwords (low motor planning) AWS and AWNS did not demonstrate significantly different levels of cortical activity. During the different syllable nonwords (high motor planning) AWS and AWNS demonstrated significantly different levels of cortical activity in two locations in the right middle frontal gyrus including Broadmann Area 9 ($t_{13} = -2.773$ $p = 0.016$), and Broadmann Area 8 ($t_{13} = -2.313$ $p = 0.038$) and the left inferior frontal gyrus approached significance ($t_{13} = -2.057$ $p = 0.06$).

Figure 7 depicts the location of significant voxel clusters that survived the family wise correction for multiple comparisons. Bar plots for each cluster are also presented.

| Region | Hem. | BA | Volume (mm ³) | F _{6, 168} | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|---------------------------|---------------------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Frontal Gyrus | Right | 45 | 2056 | 5.5865 | 0.0573 | -51.5 | -27.5 | 27.6 |
| Inferior Frontal Gyrus | Left | 44 | 1120 | 5.2016 | 0.0533 | 52.3 | -15.7 | 30.2 |
| Middle Frontal Gyrus | Right | 9 | 600 | 4.9317 | 0.0658 | -49 | -14.6 | 47.7 |
| Precentral Gyrus | Left | 6 | 248 | 4.8687 | 0.0793 | 45.3 | 9.1 | 53.4 |
| Middle Frontal Gyrus | Right | 8 | 40 | 5.1443 | 0.5622 | -46 | -17 | 53.3 |
| Precentral Gyrus | Right | 6 | 40 | 4.6267 | 0.0956 | -23.6 | 12 | 74.4 |

Table 10. Results from condition x group interaction differences between the repeated syllable and different syllable nonwords in the Motor Planning task among AWNS and AWS.

Discussion.

The primary results from the motor planning task are as follows and indicate that AWS demonstrated atypical cortical activity related to motor planning bilaterally in the left inferior frontal gyrus, middle frontal gyrus and precentral gyrus. These results are consistent with previous investigations of speech motor planning and AWS (Lu, Chen, et al., 2010). This discussion will primarily focus on the results depicting between group differences in motor planning for several reasons: 1) between group differences is one of the primary purposes of the task and 2) significant voxel clusters from the main effect that overlap with voxel clusters of the interaction effect (cf. left inferior frontal gyrus) are subsumed by the interaction.

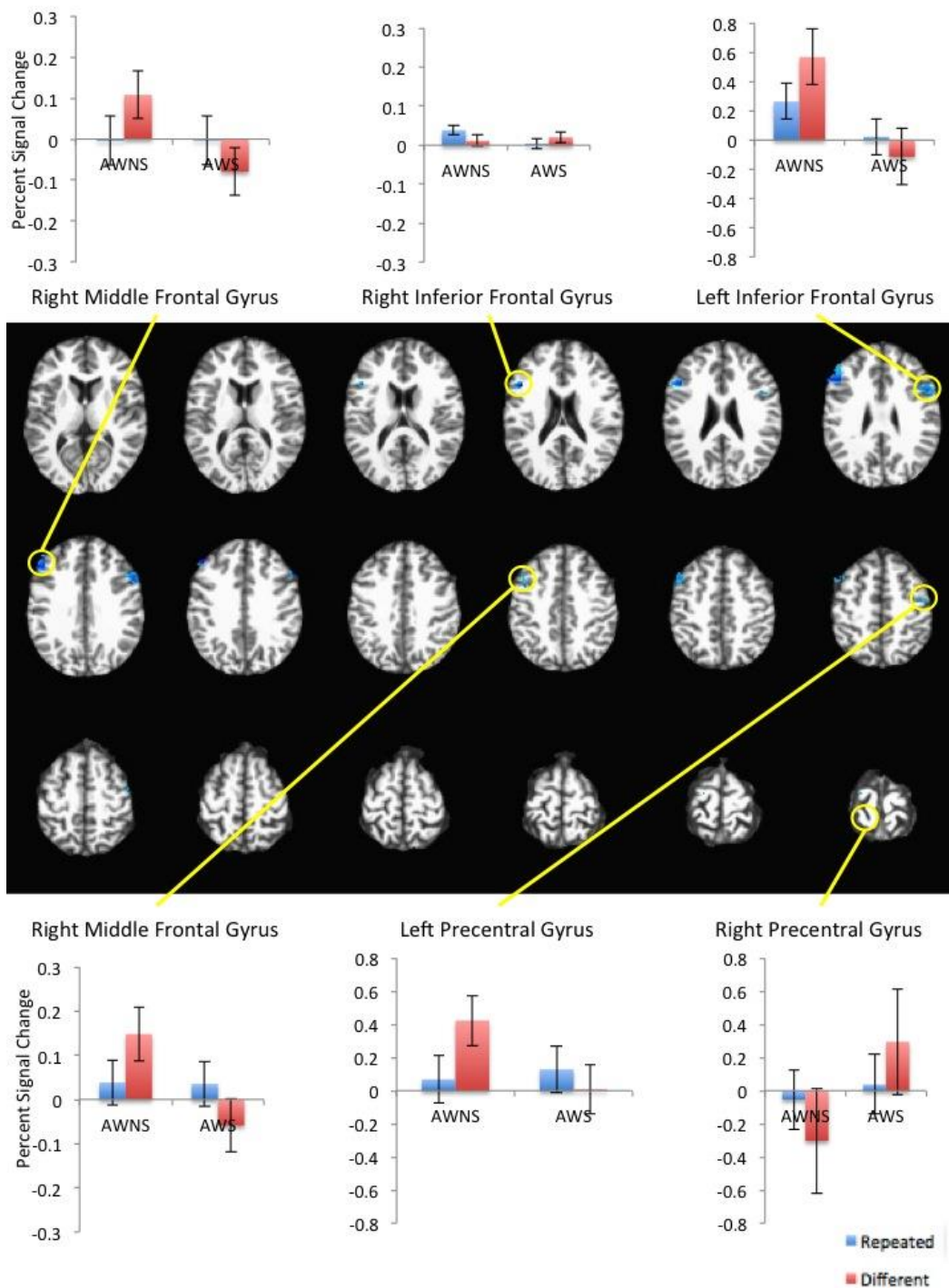


Figure 7. Clusters demonstrating significant condition x group interaction effect in Motor Planning among Adults.

Activity related to repeated syllable nonwords is in blue while activity related to different syllable nonwords is in red. In each graph the AWNS are presented in the left columns while AWS are presented in the right. Please note that the graphs have two in order to accommodate vastly different HbO signals.

The difference between the repeated syllable nonwords and different syllable nonwords was designed to elucidate regions of interest related to speech-motor planning. Both types of nonwords had a similar degree of motor execution: three syllables. However, the number of syllables necessary to plan differed between them. Only one syllable was required to be planned in the repeated syllable nonwords while the different syllable nonwords required three unique syllables to be planned. As such cortical activity in regions that demonstrated a significant difference between the two types of nonwords was related to speech-motor planning and not speech-motor execution.

Inferior Frontal Gyrus.

Previous reports have suggested that the left inferior frontal gyrus is strongly related to atypical speech-motor planning in AWS (Lu, Chen, et al., 2010). The results of the current study have confirmed this in a nonword repetition task. The left inferior frontal gyrus has been an area of great interest related to speech production. In the stuttering literature the co-activation of left and right inferior frontal gyri has led some to conclude that the right hemisphere activity is compensatory for the left hemisphere (reduced function in the left hemisphere is hypothesized from reduced gray matter volume in the left inferior frontal gyrus in school age CWS (Chang, et al., 2009).

A great deal of attention has been devoted to the increased right hemisphere activity during speech and language production among AWS. However, decreased left hemisphere activity and increased right hemisphere activity is not sufficient to accurately describe differences between stuttering and typically fluent

populations—AWS are not the only population to show anatomical and function differences in the activity of the inferior frontal gyri. Left-hand dominant speakers demonstrate a reduction in the volumetric asymmetry of both component parts of Broca's area: pars triangularis (BA 45) and pars opercularis (BA 44; Foundas, Eure, Luevano, Weinberger, 1998; Foundas, Leonard & Heilman, 1995). In addition to the anatomical asymmetries, some left-hand dominant speakers demonstrate a shift in the functional activity for language (Goodglass & Quadfasel 1954). Other clinical populations demonstrate atypical laterality of cortical activity in the pars triangularis or pars opercularis related to language including children with specific language impairment (De Guibert, Maumet, Jannin, Ferre, Treguier, Bariollot, Biraben, 2011) and high-functioning autism (Just, Cherkassky, Keller, Minshew, 2004). These reports indicate that altered laterality of the inferior frontal gyrus is not specific to stuttering. Therefore, increased right hemisphere activity is not independently sufficient to explain the disorder of stuttering. As such, paying particular attention the function of the inferior frontal gyri is essential to determine differences in cortical activity related to speech-motor planning.

The current task used nonwords in an attempt to limit cortical activity related to semantic encoding. Previous reports of functional cortical activity in the pars opercularis and pars triangularis have indicated that activity in both regions is related to phonological and semantic encoding (Devlin, Matthews & Poldrack, 2003; Poldrack, Wagner, Prull, Desmond, Glover & Gabrieli, 1999). However, other reports have indicated that the pars opercularis is related to phonological encoding while the pars triangularis is related to semantic encoding (Nixon, Lazarova, Hodinott-Hill,

Gough & Passingham., 2004). The results from the current study indicate that AWS demonstrate reduced cortical activity in the left pars opercularis during a task with limited semantic processing but high phonological processing. The reduced activity in the left inferior frontal gyrus during nonwords requiring high motor planning demand may indicate that AWS demonstrate subtly reduced phonological processing abilities than AWNS. Further evidence for subtle reductions in phonological processing come from behavioral results from nonword repetition tasks. While AWS and AWNS demonstrate similar degrees of accuracy in nonword repetition tasks as the nonwords increase in syllable length increase AWS were significantly less accurate during initial attempts and required more attempts to achieve correct production of nonwords (Byrd, Vallely, Anderson & Sussman., 2012). These results suggest that the atypical speech motor planning in the left inferior frontal gyrus is related to phonological processing. Only correct and fluently produced nonwords were included in the analysis, therefore the differences observed here likely reflects activity related to atypical speech-motor planning and not activity related to overt stuttering behavior.

According to the Directions Into Velocities of Articulators (DIVA) Model (Guenther, Ghosh & Tourville, 2006; Tourville & Guenther, 2011) the left hemisphere pars opercularis contains speech sound maps which are necessary for feed-forward models of speech-motor control (see Figure 1). Similarly, the right inferior frontal gyrus is involved in the feedback control network, indicating its involvement in negative feedback models of speech-motor control. Reduced activity in the left inferior frontal gyrus indicates that AWS may demonstrate insufficient

feedforward models of speech production. As predicted by Civier et al., (2011) and Max, et al., (2004) inefficient feedforward models may force AWS to rely more heavily on negative feedback methods of motor control. According to the DIVA model a cortical region essential for feedback control is the right premotor cortex and the right inferior frontal gyrus (pars opercularis). These regions integrate errors signals from the articulatory error map (Heschl's Gyrus, posterior superior temporal gyrus) and the somatosensory error map (ventral post central gyrus, supramarginal gyrus). If the errors maps include an error that supersedes an acceptable threshold a breaking of speech production may occur (Xue, Aron, Poldrack, 2008).

A motor control system that is over-reliant on incoming acoustic and or proprioceptive feedback may result in increased activity in the right inferior frontal gyrus—that is more frequent and correction of errors may increase the activity in the right inferior frontal gyrus. Taken together, previously reported increased activity in the right inferior frontal gyrus may not be compensatory, but simply the proper function of the neural networks related to speech-motor control. However, the differential response between repeated and different syllable nonwords indicates that activity in the right inferior frontal gyrus is related to speech-motor planning. The planning task required both speech-motor planning and execution. If activity in the right inferior frontal gyrus is related to breaking of speech due the proper detection of errors the same differences should be observed in motor execution.

Middle Frontal and Precentral Gyri.

Activity in the middle frontal gyrus (BA 9) is associated with prosody (Meyer, Steinhauer, Alter, Friederici & von Cramon, 2004). The nonwords in the present study unintentionally differed in prosody. Each syllable in the repeated syllable nonwords had similar prosodic stress on each syllable. In the different syllable nonwords, however, the syllables had more varied prosodic stress. This was unintentional; as such the present study may have unintentionally identified regions related to prosody. That AWS demonstrated significant reductions in cortical activity related to prosody is a novel finding in stuttering research. This reduction in right middle frontal gyrus activity related to prosody in conjunction with reduced activity in the left hemisphere inferior frontal gyrus related to motor planning might reflect a lack of specialization of the frontal lobes for speech production associated with stuttering. However, in order to be certain that this activity is related to prosody future research should specifically examine cortical activity related to prosody in AWS.

In addition to the inferior and middle frontal gyri, AWS demonstrated atypical cortical activity related to speech-motor planning in the precentral gyrus. Among AWS these differences can be characterized by decreased activity in the left hemisphere and marginally increased activity in the right hemisphere relative to AWNS. The left hemisphere precentral region is located in the face and mouth representation. Given the reduced activity in the left inferior frontal gyrus the reduced activity may be related to a reduction in the degree of speech-motor planning activity. However, the decreased activity may also be related to inefficient

connections between the inferior frontal gyrus and the precentral gyrus. AWS have demonstrated reductions in diffusion tensor imaging (DTI) observed in the laryngeal and tongue representation (Sommer et al., 2003) and in the connections between the inferior frontal gyrus and the precentral gyrus (Chang, et al., 2011).

Summary.

The results from the motor planning task indicate that AWS atypical motor planning in the left inferior frontal gyrus. These results suggest that left inferior frontal gyrus is a particularly important region complicit for speech-motor planning. Drawing from the DIVA model, inefficient feedforward commands resulting in increased reliance on negative feedback models of speech-motor control would results in increased activity in the right inferior frontal gyrus. AWS also demonstrate reduced cortical activity related to prosody in the right middle frontal gyrus. Taken together these results suggest that the differences in cortical activity observed in AWS may reflect a lack of specialization of the frontal lobes for speech production.

Motor Planning: Children.

Within Group Differences.

Results from the ANOVA identified seven clusters of voxels demonstrating a significant difference between repeated and different syllable nonwords that survived the family wise correction for multiple comparisons. These clusters are presented in Table 11.

Averaged across groups, increased speech-motor planning demand (different syllable nonwords) was associated with an increase in HbO in the right precentral

gyrus and bilaterally in the middle frontal gyrus. Increased motor planning demand was associated with decreased HbO in the right middle frontal gyrus, inferior parietal lobule and post central gyrus. Figure 8 depicts significant voxel clusters that survived the correction for multiple comparisons. The number of significant clusters where the activity during the repeated syllable nonwords is greater than the different syllable nonwords. This was unexpected; however, may be due to the differences in the nonword stimuli. The different syllable nonwords the fundamental frequency and syllabic stress varied within the nonwords, whereas, the syllables in the repeated syllable nonwords had similar fundamental frequency and the syllabic stress did not vary.

| Region | Hem. | BA | Volume (mm ³) | F _{7, 48} | SEM | Talarach Coordinates (RAI) | | |
|-----------------------------|--------------|----------|---------------------------|--------------------|---------------|----------------------------|--------------|-------------|
| | | | | | | x | y | z |
| Middle Frontal Gyrus | Right | 9 | 1872 | 7.251 | 0.1034 | -39.4 | -12.8 | 45.3 |
| Inferior Parietal Lobule | Right | 40 | 1096 | 7.95 | 0.1802 | -48.6 | 42.6 | 57.3 |
| Post central Gyrus | Left | 3 | 504 | 6.4398 | 0.1707 | 60.3 | 15.6 | 31.8 |
| Post central Gyrus | Right | 1 | 176 | 7.0564 | 0.3002 | -59.6 | 27.1 | 39.3 |
| Middle Frontal Gyrus | Left | 9 | 136 | 6.0426 | 0.2621 | 44 | -5.4 | 40.9 |
| Middle Frontal Gyrus | Left | 9 | 96 | 5.6188 | 0.1126 | 42.9 | -21.8 | 36.3 |
| Precentral Gyrus | Right | 6 | 48 | 6.117 | 0.4131 | -51.6 | 11.4 | 34 |

Table 11. Results from condition differences between the repeated syllable and different syllable nonwords in the Motor Planning task among CWNS and CWS. Bolded clusters indicate regions where different syllable nonwords > repeated syllable nonwords.

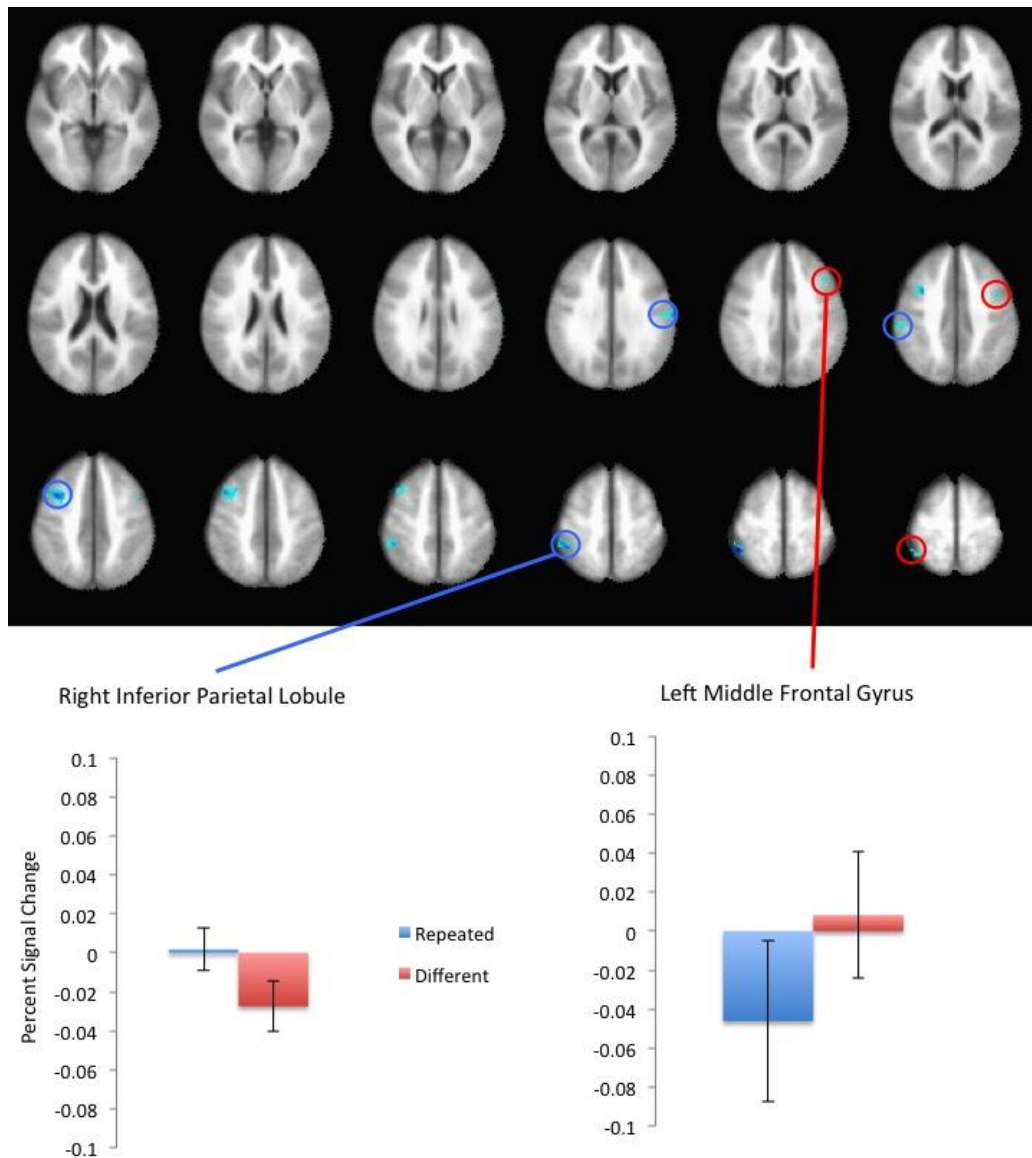


Figure 8. Clusters demonstrating significant condition effect among Children in Motor Planning. Activity related to repeated syllable nonwords are presented with red circles while activity related to different syllable nonwords is presented with blue circles.

Between Group Differences.

Results from the ANOVA identified six clusters of voxels demonstrating a significant difference in HbO between CWS and CWNS that survived the family wise correction for multiple comparisons. These clusters are presented in Table 12.

Averaged across conditions, CWS demonstrated increased HbO relative to CWNS in the right and left middle frontal gyrus. CWS demonstrated decreased HbO relative to CWNS in the left superior frontal gyrus, middle frontal gyrus, right inferior and superior parietal lobules. As with the adults, these regions do not reflect regions of atypical motor planning, but regions of increased or decreased activity without respect for motor planning. Figure 9 presents the group differences in HbO averaged across repeated and different syllable nonwords.

| Region | Hem. | BA | Volume (mm ³) | F _{6, 41} | SEM | Talarach Coordinates (RAI) | | |
|---------------------------------|--------------|-----------|---------------------------|--------------------|---------------|----------------------------|-------------|-------------|
| | | | | | | x | y | z |
| Superior Frontal Gyrus | Left | 6 | 1784 | 8.059 | 0.159 | 17 | 15.9 | 73.2 |
| Middle Frontal Gyrus | Right | 6 | 936 | 7.2394 | 0.181 | -30.4 | 10.5 | 65.5 |
| Middle Frontal Gyrus | Left | 9 | 800 | 7.8781 | 0.2059 | 45.6 | -4.2 | 39.6 |
| Middle Frontal Gyrus | Left | 6 | 512 | 5.9564 | 0.0769 | 25.2 | -2.3 | 63.5 |
| Inferior Parietal Lobule | Right | 40 | 200 | 6.4392 | 0.2238 | -53 | 29.2 | 42.4 |
| Superior Parietal Lobule | Right | 5 | 40 | 5.1297 | 0.0832 | -38.8 | 47.6 | 66 |

Table 12. Results from group differences between the repeated syllable and different syllable nonwords in the Motor Planning task among CWNS and CWS.

Bolded clusters indicate regions where CWNS > CWS.

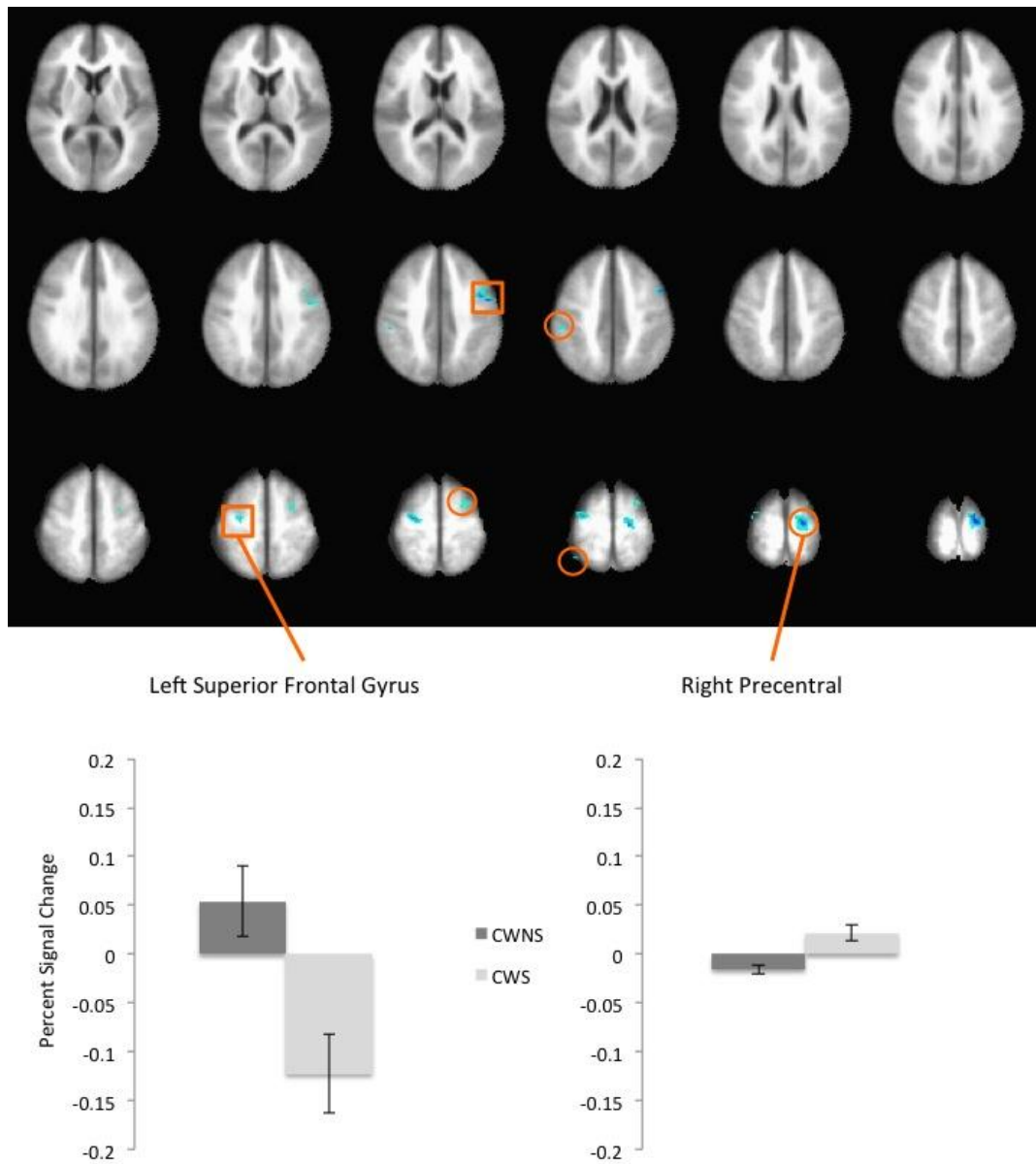


Figure 9. Clusters demonstrating a significant group effect in Motor Planning among Children. Clusters where CWS > CWNS are depicted with a circle, while clusters where AWS < AWNS are depicted with a square.

Between Group Differences in Motor Planning.

The interaction term was used to identify clusters where CWS and CWNS demonstrated different patterns of cortical activity between the conditions. The ANOVA results from the group by condition interaction term reflect regions of atypical speech-motor planning among CWS. Results from the ANOVA identified three clusters of voxels that survived the correction for multiple comparisons. These clusters are presented in Table 13.

Among CWNS, increased speech-motor planning demand was associated with reduced HbO in the right inferior frontal gyrus and an increase in left post central gyrus. In those same regions, CWS demonstrated the opposite trend with an increased HbO in the right inferior frontal gyrus and decreased in the left post central gyrus. Additionally, among CWS increased motor planning was associated with decreased activity in the right middle frontal gyrus, whereas there was no difference between repeated and different syllable nonwords in CWNS.

Post hoc t-tests were completed to determine if CWS and CWNS demonstrated significantly different levels of cortical activity during each condition at each significant cluster. One cluster demonstrated significant differences between the groups. During different syllable nonwords CWS demonstrated significantly increased HbO in the right middle frontal gyrus relative to CWNS.

These findings, particularly that of the inferior frontal gyrus, are consistent with previous reports of cortical activity during speech production in AWS. Figure 10 presents the clusters demonstrating a significant interaction effect between

condition (repeated / different syllable nonwords) and group. These findings are consistent with the activity in the current study obtained from AWS.

| Region | Hem. | BA | Volume (mm ³) | F _{3, 20} | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|---------------------------|--------------------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Frontal Gyrus | Right | 45 | 1080 | 7.4932 | 0.1648 | -45.9 | -24.2 | 25 |
| Post central Gyrus | Left | 3 | 48 | 5.2985 | 0.1001 | 61 | 18.6 | 34 |
| Middle Frontal Gyrus | Right | 9 | 48 | 5.1089 | 0.0237 | -38.3 | -6.7 | 39.7 |

Table 13. Results from condition x group interaction differences between the repeated syllable and different syllable nonwords in the Motor Planning task among CWNS and CWS.

Discussion.

The primary results of this task indicated that increased speech-motor planning demand was associated with increased activity in the right inferior frontal gyrus among CWS. This is consistent with previous reports of cortical activity in AWS (Lu, Chen, et al., 2010) as well as the current study. Additionally, increased speech-motor planning demand was associated with decreased activity in the right middle frontal gyrus and increased speech-motor planning demand was associated with increased activity in the left post central gyrus among CWNS relative to CWS.

Increased speech-motor planning demand is associated with increased activity in the right inferior frontal gyrus (BA45) and decreased activity in the right middle frontal gyrus (BA 9) in both AWS and CWS. This suggests that these differences in cortical activity are established by the school-age years.

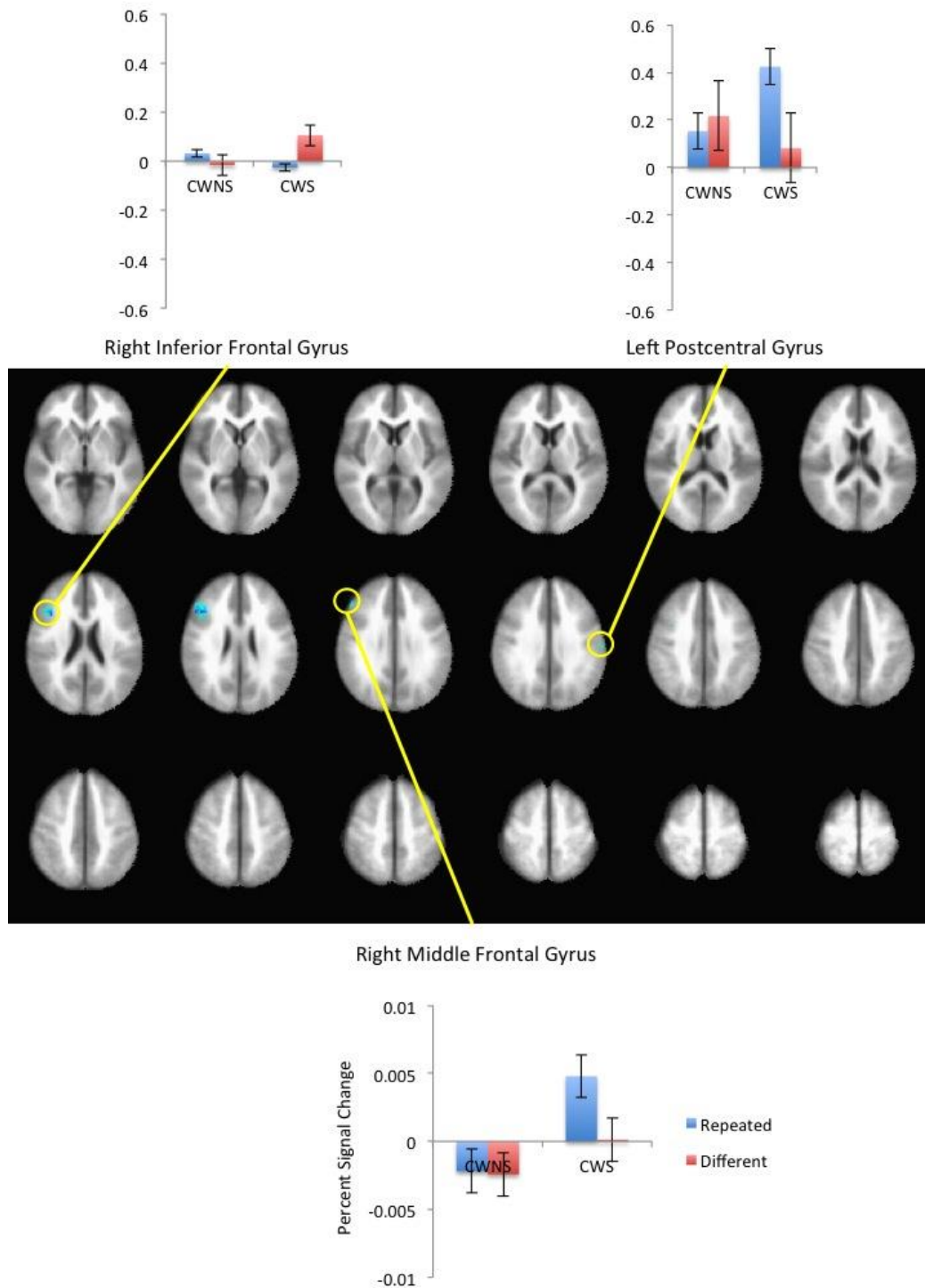


Figure 10. Clusters demonstrating significant condition x group interaction effect in Motor Planning among Children. Activity related to repeated syllable nonwords is in blue while activity related to different syllable nonwords is in red. In each graph the CWNS are presented in the left columns while CWS are presented in the right. Please note that the graphs have two in order to accommodate vastly different HbO signals.

Right Inferior Frontal Gyrus.

Activity in the right inferior frontal gyrus (BA 45) has been associated with inhibition of voluntary behaviors (Aron, Fletcher, Bullmore, Shallice, & Robbins, 2003; Aron, Robbins & Poldrack, 2004). Increased activity in BA 45 during fluent speech production may indicate that both AWS and CWS are more susceptible to inhibitory response of the right inferior frontal gyrus. Others have hypothesized that increased activity in the right inferior frontal gyrus may be playing a compensatory role for reduced activity in the left hemisphere (Preibisch, Neumann, et al., 2003, Lu, Chen, et al., 2010). Examination of activity in BA 45 during speech-motor execution may elucidate the nature of increased activity in BA 45.

If the right BA 45 is disrupting speech production through inhibition of speech, the inhibition may be causing delay in the assembly of the motor plan. According to EXPLAN (Howell, Au-Yeung, 2002) stuttering may emerge as a result of a motor plan that is not complete when execution begins. Alternatively, if BA 45 is playing a compensatory role for left hemisphere dysfunction then activity in BA 45 may be related to semantic encoding, given that the left BA 45 plays a role is thought to contribute to semantic encoding (Devlin, et al., 2003; Poldrack, et al., 1999). This is intriguing given that nonwords were used specifically to limit semantic encoding. However, activity related to semantic encoding is not surprising given that repetition of nonwords is a commonly used tool to identify children with specific language impairment (Coady & Evans, 2008).

Middle Frontal Gyrus.

In both AWS and CWS increased speech–motor planning demand was associated with decreased activity in the right middle frontal gyrus (BA 9); whereas AWNS demonstrated increased activity in the right middle frontal gyrus. Activity in the right middle frontal gyrus has been associated with prosody (Meyer et al., 2004). Few studies have reported between group differences in activity in the middle frontal gyrus (Neumann, et al., 2003, Preibisch, Neumann, et al., 2003), as such the literature is silent on potential contribution of increased activity in the right middle frontal gyrus. Taken together with decreased activity in the left inferior frontal gyrus in AWS and increased activity in the right inferior frontal gyrus in AWS and CWS may suggest a lack of specialization of the frontal lobes for speech production.

Between Age Comparisons.

The similarities of the results between adults and children are striking. And while it would be tempting to directly compare these results, between-group analysis of cortical activity is not yet possible due to the fact that the head spaces are in different atlases. Different atlases were required because of developmental changes in brain structure. Due to the fact that different atlases were used it is not possible to register them together in order to determine if regions of activation overlap. The means exist to reframe the images to each other and determine if regions overlap, however, these steps have yet to be developed and implemented.

Motor Execution: Adults

Within Group Differences.

Results from the ANOVA identified 13 clusters of voxels demonstrating significant differences between covert and overt naming tasks that survived the family wise correction for multiple comparisons. These clusters are presented in Table 14.

Averaged across groups, clusters demonstrating increased HbO in the overt naming condition relative to the covert naming condition included the left inferior parietal lobule, inferior frontal gyrus, post central gyrus, middle frontal gyrus, right superior temporal gyrus, inferior parietal lobule, and precentral gyrus. Clusters demonstrating increased HbO in the covert relative to overt naming condition included the left precentral gyrus, left supplementary motor area and the right middle frontal gyrus.

Figure 11 depicts the location of the voxel clusters. Clusters demonstrating increased HbO in covert naming are identified with a red circle while clusters demonstrating increased HbO in overt naming are identified with a blue circle. Regions associated with increased activity in overt naming include regions that are related to speech production. Regions demonstrated increased activity to overt naming are those commonly associated with speech production networks.

| Region | Hem. | BA | Volume (mm ³) | F _{13, 376} | SEM | Talarach Coordinates (RAI) | | |
|---------------------------------|--------------|-----------|---------------------------|----------------------|---------------|----------------------------|--------------|-------------|
| | | | | | | x | y | z |
| Inferior Parietal Lobule | Left | 40 | 1408 | 5.143 | 0.0493 | 54.6 | 35.1 | 41.1 |
| Inferior Frontal Gyrus | Left | 45 | 1344 | 6.6068 | 0.1361 | 54.9 | -30.3 | 2 |
| Precentral Gyrus | Left | 4 | 288 | 5.2527 | 0.1469 | 55.9 | 16.2 | 42.5 |
| SMA | Left | 6 | 264 | 5.7668 | 0.2195 | 6.9 | 16.3 | 81.7 |
| Post central Gyrus | Left | 3 | 224 | 4.695 | 0.0731 | 24.6 | 34.1 | 74.5 |
| Superior Temporal Gyrus | Right | 22 | 200 | 4.64 | 0.053 | -71.3 | 27.9 | 0 |
| Middle Frontal | Right | 6 | 120 | 4.3526 | 0.0371 | -31.1 | 6.6 | 72.5 |
| Middle Frontal Gyrus | Left | 9 | 112 | 4.4819 | 0.0449 | 48.1 | -14.2 | 33.9 |
| Inferior Parietal Lobule | Right | 40 | 80 | 4.4869 | 0.0471 | -64.6 | 44 | 22.8 |
| Middle Frontal Gyrus | Left | 9 | 80 | 4.571 | 0.0573 | 43.8 | -12.4 | 31.2 |
| Precentral | Right | 4 | 72 | 4.8434 | 0.1855 | -54.4 | 16 | 33 |
| Middle Frontal | Left | 9 | 40 | 4.5587 | 0.1068 | 41.9 | -18 | 36 |
| Middle Frontal Gyrus | Right | 46 | 40 | 4.2921 | 0.0255 | -48.8 | -31.6 | 38.4 |

Table 14. Results from condition differences between the covert and overt naming conditions in the Motor Execution task among AWNS and AWS.

Bolded clusters indicate regions where overt naming > covert naming.

Between Group Differences.

Results from the ANOVA identified eight clusters of voxels demonstrating a significant difference in HbO between AWS and AWNS that survived the family wise correction for multiple comparisons. These clusters are presented in Table 15.

Averaged across covert and overt naming conditions clusters demonstrate increased HbO among AWS relative to AWNS include the left precentral gyrus and the right post central gyrus. Clusters where AWS demonstrated reduced HbO relative to AWNS include the left supplementary motor area, inferior frontal gyrus, and the right precentral gyrus. Figure 12 depicts the location of voxel clusters demonstrating group differences in HbO. Note that clusters where AWS > AWNS are depicted by orange circles where as AWS < AWNS are depicted by orange squares. Relative to AWNS, AWS demonstrate reduced activity in the left inferior frontal gyrus and supplementary motor area. This is consistent with previous research.

Interestingly, AWS demonstrated increased activity at several regions within the right postcentral gyrus. While other reports have documented differences in the postcentral gyrus (Lu, Chen, et al., 2010), it is not a commonly reported region.

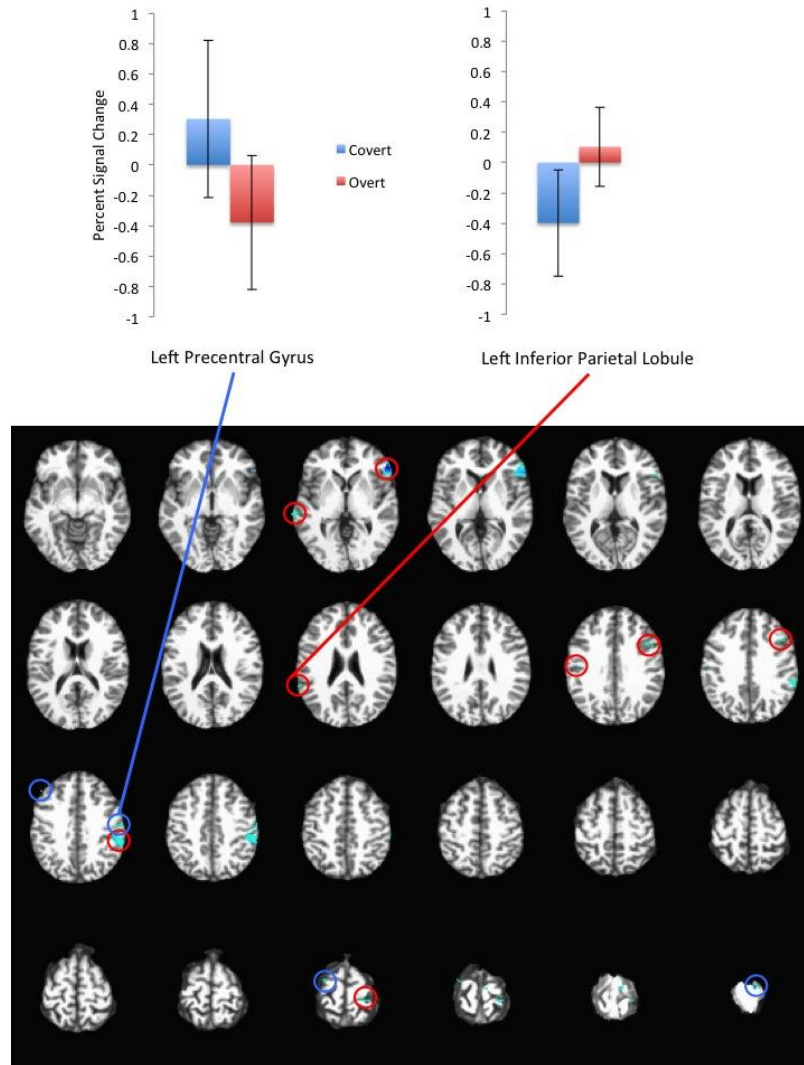


Figure 11. Clusters demonstrating significant condition effect among Adults in Motor Execution. Activity related to covert naming is presented with red circles while activity related to overt naming is

presented with blue circles

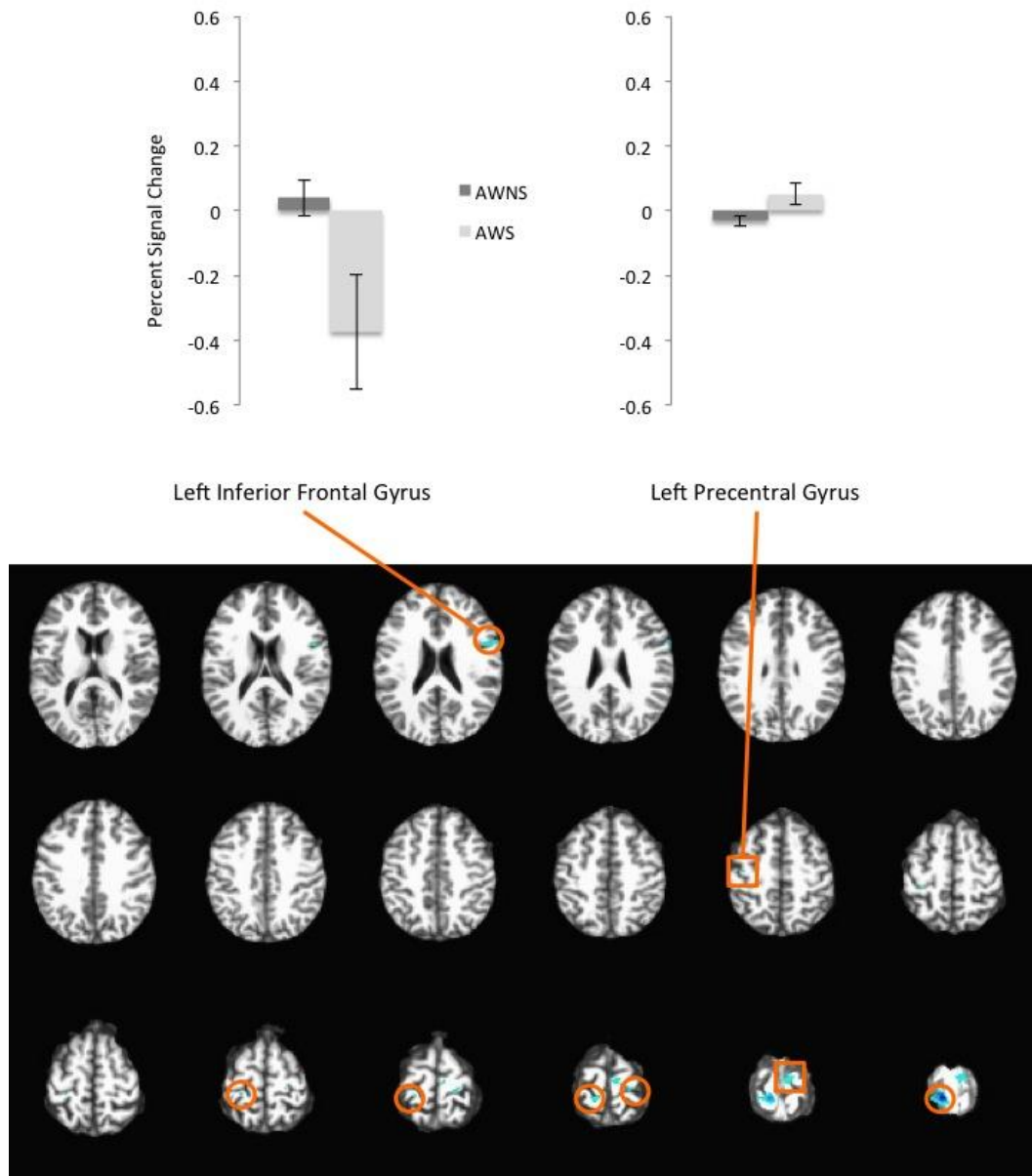


Figure 12. Clusters demonstrating a significant group effect in Motor Execution among Adults. Clusters where AWS > AWNS are depicted with a circle, while clusters where AWS < AWNS are depicted with a square.

Between Group Differences in Motor Execution.

The interaction term was used to identify voxel clusters where AWS and AWNS demonstrated different patterns of cortical activity between covert and overt naming conditions. The ANOVA results from the group by condition interaction term reflect regions of atypical speech-motor planning among AWS. Results from the ANOVA identified eight clusters that survived the correction for multiple comparisons. These clusters are presented in Table 16.

| Region | Hem. | BA | Volume (mm ³) | F _{8, 231} | SEM | Talarach Coordinates (RAI) | | |
|-------------------------------|--------------|----------|---------------------------|---------------------|---------------|----------------------------|-------------|-------------|
| | | | | | | x | y | z |
| Post central Gyrus | Right | 1 | 1408 | 6.1879 | 0.128 | -13.8 | 38.5 | 80.2 |
| SMA | Left | 6 | 832 | 4.8727 | 0.0483 | 6.5 | 18.3 | 79.2 |
| Inferior Frontal Gyrus | Left | 9 | 352 | 5.0503 | 0.0924 | 54.8 | -7.4 | 22 |
| Precentral Gyrus | Left | 4 | 176 | 4.7746 | 0.0827 | 20.2 | 28.9 | 70.9 |
| Post central Gyrus | Right | 3 | 56 | 4.4441 | 0.0797 | -26 | 36 | 70 |
| Post central Gyrus | Right | 3 | 48 | 4.3948 | 0.0848 | -28.3 | 34 | 65 |
| Precentral Gyrus | Right | 4 | 40 | 4.6671 | 0.0611 | -41.2 | 16 | 53.6 |
| Post central Gyrus | Right | 3 | 40 | 4.3847 | 0.0508 | -34.4 | 34 | 59.2 |

Table 15. Results from group differences between the covert and overt naming conditions in the Motor Execution task among AWNS and AWS.

Bolded clusters indicate regions where AWNS > AWS.

Among AWNS, speech-motor execution was associated with reduced HbO in the left precentral gyrus, inferior frontal gyrus (BA 45) and the right post central gyrus. AWNS demonstrated increased HbO in the left inferior (BA 44) and middle frontal gyri, precentral gyrus, post central gyrus and the right supramarginal gyrus. In those same regions, however, AWS demonstrated the opposite trend, demonstrating increased HbO in left precentral gyrus, inferior frontal gyrus and the right post central gyrus and decreased in the left inferior and middle frontal gyri, precentral gyrus, post central gyrus and the right supramarginal gyrus.

Post hoc t-tests were completed to determine if AWS and AWNS demonstrated significantly different levels of HbO during each condition at each significant cluster. AWS and AWNS demonstrated significantly different levels of HbO in two clusters. During covert naming AWS demonstrated significantly more HbO than AWNS in the left inferior frontal gyrus (BA 45, $t_{14} = 2.301$ $p = 0.037$) and significantly less HbO in the right post central gyrus ($t_{14} = 2.809$ $p = 0.014$). AWS also demonstrated less HbO than AWNS in the right supramarginal gyrus in overt naming, a difference that approached significance ($t_{14} = 2.061$ $p = 0.058$). Figure 13 depicts clusters demonstrating significant interaction effects between condition (covert/overt naming and group).

| Region | Hem. | BA | Volume (mm ³) | F _{11, 318} | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|---------------------------|----------------------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Frontal Gyrus | Left | 45 | 3064 | 5.8457 | 0.0578 | 56.5 | -17.3 | 1.3 |
| Precentral Gyrus | Left | 4 | 1792 | 5.171 | 0.0461 | 55.4 | 10.9 | 36.3 |
| Precentral Gyrus | Left | 6 | 392 | 4.8737 | 0.0625 | 44.8 | 1.6 | 48.9 |
| Middle Frontal Gyrus | Left | 6 | 368 | 4.5024 | 0.0275 | 35.5 | -14.3 | 48.9 |
| Supramarginal Gyrus | Right | 40 | 184 | 4.3718 | 0.0243 | -57.9 | 48.6 | 36.3 |
| Inferior Frontal Gyrus | Left | 44 | 136 | 4.8702 | 0.1167 | 58.3 | -12.5 | 20.8 |
| Post central Gyrus | Right | 3 | 96 | 5.1966 | 0.2303 | -54.5 | 14.6 | 53.6 |
| Post central Gyrus | Left | 3 | 88 | 4.3474 | 0.043 | 45.7 | 20.5 | 57.7 |

Table 16. Results from condition x group interaction differences between the covert and overt naming conditions in the Motor Execution task among AWNS and AWS.

Discussion.

The primary results of this experiment indicate that AWS demonstrate atypical cortical activity associated with speech-motor execution as reflected by HbO in the left inferior frontal gyrus, in BA 44 and BA 45. AWS also demonstrate clusters of atypical speech-motor execution in the right supramarginal gyrus, bilaterally and in the pre- and post central gyri.

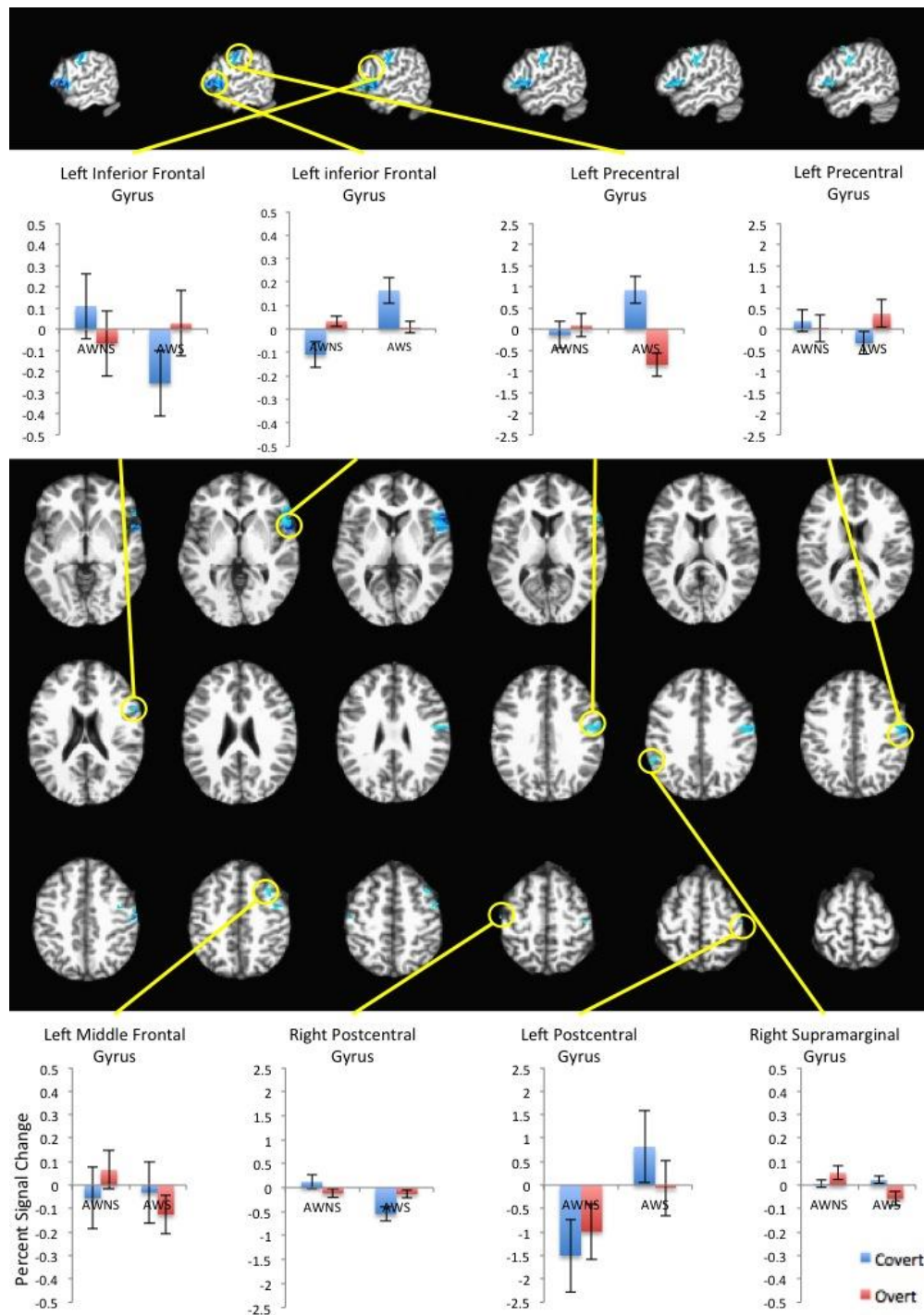


Figure 13. Clusters demonstrating significant condition x group interaction effect in Motor Execution among Adults. Activity related to covert naming is in blue while activity related to overt naming is in red. In each graph the AWNS are presented in the left columns while AWS are presented in the right. Please note that the graphs have two in order to accommodate vastly different HbO signals.

Inferior frontal gyrus.

As previously discussed the inferior frontal gyrus can be subgrouped into two component parts the pars opercularis (BA 44) and the pars triangularis (BA 45). In pars opercularis, AWNS demonstrated an increase in cortical activity during overt naming relative to covert naming whereas AWS demonstrated a decrease. In pars opercularis, AWNS demonstrated an increase in cortical activity during overt naming relative to covert naming whereas AWS demonstrated a decrease. Activity in the pars opercularis has been demonstrated to be related to phonological encoding (Devlin et al., 2003, Poldrack et al., 1999).

According to the DIVA model, speech-sound maps necessary for feed-forward models of speech-motor control are located in the left pars opercularis (Guenther, Ghosh & Tourville, 2006; Tourville & Guenther, 2011). Increased activity in the pars opercularis in AWNS may reflect activity related to the execution of the articulatory plan, that is, the implementation of speech-sound maps during ongoing speech production. The reduced activity demonstrated by AWS may reflect weaker utilization of speech-sound maps. The given task is not possible to determine if the speech-sound maps of AWS are less well established or if they are not fully activated during speech production. However, this is not germane to the discussion at hand. What is essential is these reduced activity in the pars opercularis reflects unstable feed-forward mechanisms of speech-motor control.

Unstable feedforward mechanisms of speech-motor control have been implicated in a causal role of disfluencies (Civier, et al., 2010). The current study only analyzed fluently produced utterances. As such, the current study cannot

confirm the findings of Civier et al., (2011); it does, however, suggest that AWS do indeed poses weaker feed-forward models of speech-motor control. Several participants produced both fluent and disfluent trials; future investigations could examine the cortical activity associated with disfluent speech production.

Recall that during the motor planning task AWS demonstrated increased activity in the right inferior frontal gyrus. It was determined that increased activity in the right inferior frontal gyrus would suggest that this activity is related to inhibitory breaking of speech production. However, AWS did not demonstrate atypical activity related to motor execution in the right inferior frontal gyrus. This indicates that the increased right inferior frontal gyrus observed in AWS is related to speech-motor planning. As such, is likely compensatory for inefficient planning in the left hemisphere. These results confirm the findings of Lu, Chen, et al., (2010) and Preibisch et al., (2003). Increased activity in the right hemisphere is compensatory and potentially related to inefficient speech-motor planning in the left inferior frontal gyrus.

Supramarginal Gyrus.

Both the left and right supramarginal gyri are necessary for phonological processing (Hartwigsen, Baumgaertner, Price, Koehnke, Ulmer, & Siebner, 2010). During TMS disruption of both the right and left supramarginal gyri resulted in reduced accuracy during phonological tasks. During overt naming, AWNS demonstrated increased activity in the right supramarginal gyrus; however, during covert naming the gyrus was inactive. By contrast, during overt naming AWS

demonstrated reduced activity in the supramarginal gyrus relative to the AWNS. This suggests the potential for weaker phonological processing among AWS.

According to DIVA (Guenther, Ghosh & Tourville, 2006; Tourville & Guenther, 2011), the supramarginal gyrus is responsible several aspects of integrating proprioceptive and acoustic feedback into the neural processes of speech production. The supramarginal gyrus is proposed to contain the somatosensory target map (position of articulators for correct production), the state map (current position of articulators) and the error map (difference between the target map and the state map). These are the component parts of a negative feedback control system. The current experiment is not capable to accurately determine whether activity is related to the target map, state map or error map. However, it may suggest that AWS demonstrate reduced incoming sensory feedback for speech production.

Accurate sensory feedback is essential for establishing accurate internal representation of speech-sound maps (cf. DIVA). Inefficient accuracy of internal models to update or significantly active feed-forward models has been suggested to causally contribute to the development of stuttering in children (Max et al., 2004). However, the DIVA model has not yet tested this hypothesis, as such the veracity cannot be confirmed at this time.

Motor Execution: Children

Within Group Differences.

Results from the ANOVA identified seven clusters of voxels demonstrating a significant difference between covert and overt naming tasks that survived the

family wise correction for multiple comparisons. These clusters are presented in Table 17.

Averaged across groups, motor execution is associated with increased HbO bilaterally in the precentral gyrus, and the left inferior frontal gyrus. Motor execution was associated with a decrease in HbO in the left inferior parietal lobule and the right post-central gyrus. Figure 14 presents clusters demonstrating significant condition effect.

| Region | Hem. | BA | Volume (mm3) | F7, 48 | SEM | Talarach Coordinates (RAI) | | |
|-------------------------------|--------------|-----------|--------------|---------------|---------------|----------------------------|--------------|-------------|
| | | | | | | x | y | z |
| Precentral Gyrus | Right | 4 | 2768 | 7.2897 | 14.121 | -29.5 | 19.8 | 69.9 |
| Precentral Gyrus | Left | 6 | 2384 | 6.5646 | 11.686 | 53.2 | 3.6 | 32.9 |
| Precentral Gyrus | Left | 4 | 1232 | 9.1421 | 19.038 | 42 | 16.6 | 58.5 |
| Precentral Gyrus | Right | 6 | 296 | 5.8006 | 7.1036 | -59.4 | 4.5 | 37.3 |
| Inferior Frontal Gyrus | Left | 45 | 272 | 5.7587 | 6.9252 | 50.3 | -26.7 | 14.6 |
| Inferior Parietal Lobule | Left | 40 | 112 | 5.8168 | 8.1837 | 52.6 | 36.5 | 56.2 |
| Post central Gyrus | Right | 3 | 96 | 5.6244 | 6.3744 | -39.3 | 27.1 | 52 |

Table 17. Results from condition differences between the covert and overt naming conditions in the Motor Execution task among CWNS and CWS.
Bolded clusters indicate regions where overt naming > covert naming.

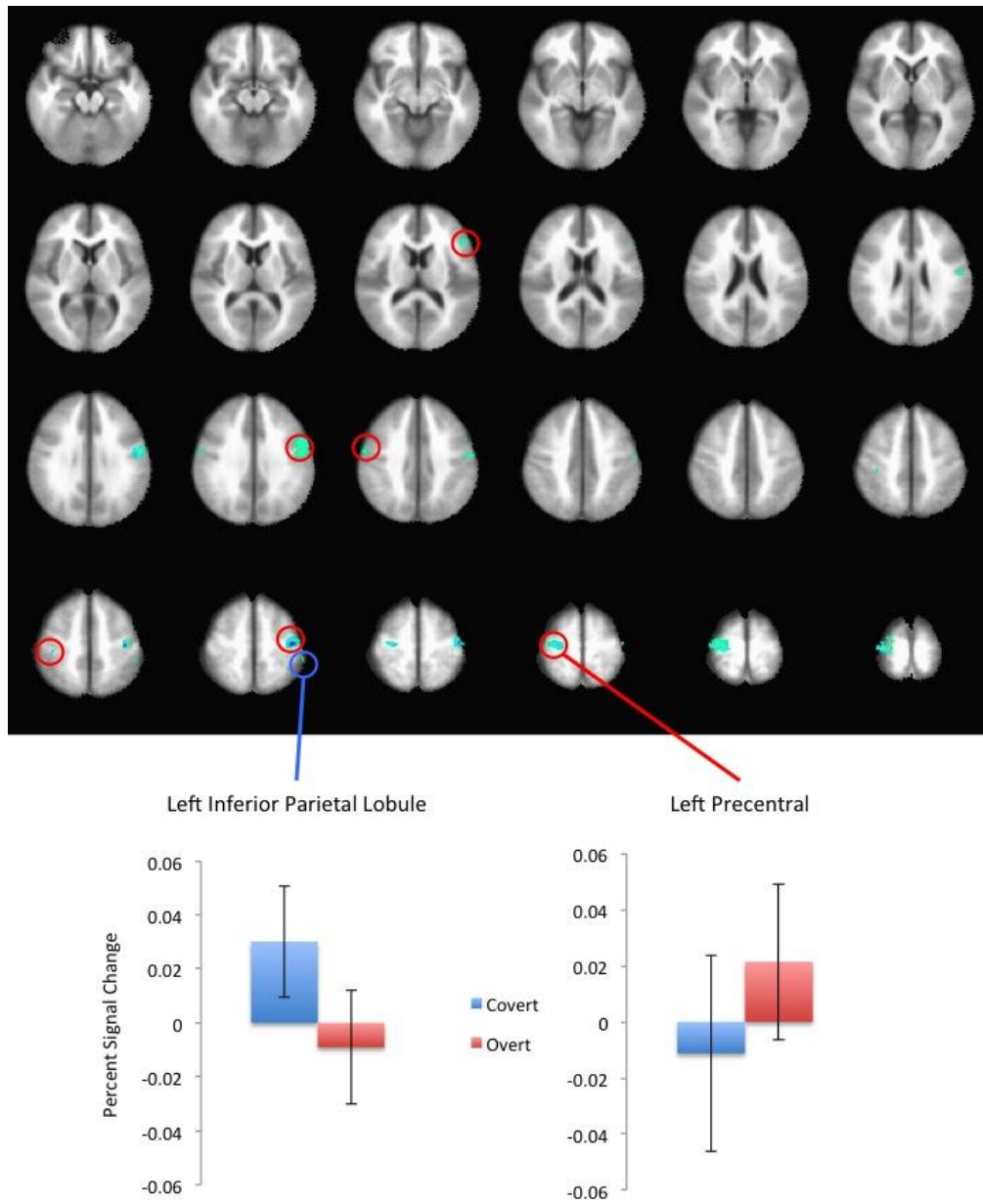


Figure 14. Clusters demonstrating significant condition effect among Children in Motor Execution. Activity related to covert naming is presented with red circles while activity related to overt naming is presented with blue circles.

Between Group Differences.

Results from the ANOVA identified four clusters of voxels demonstrating a significant difference in HbO between CWS and CWNS that survived the family wise correction for multiple comparisons. These clusters are presented in Table 18.

Averaged across overt and covert naming conditions, CWS demonstrated increased HbO relative to CWNS in the right precentral gyrus. However, CWS demonstrated reduced HbO in the left post central gyrus and bilaterally in the precentral gyrus. Figure 15 presents clusters demonstrating a significant group effect (averaged across overt and covert naming).

| Region | Hem. | BA | Volume (mm3) | F4, 27 | SEM | Talarach Coordinates (RAI) | | |
|---------------------------|--------------|----------|--------------|---------------|---------------|----------------------------|-------------|-------------|
| | | | | | | x | y | z |
| Post central Gyrus | Left | 3 | 280 | 6.8025 | 9.7442 | 48.3 | 14.2 | 51.6 |
| Precentral Gyrus | Right | 6 | 280 | 5.52 | 6.5 | -29.3 | 19 | 65.4 |
| Precentral Gyrus | Right | 6 | 216 | 8.1533 | 13.495 | -55.3 | -5.3 | 36.4 |
| Precentral Gyrus | Left | 6 | 120 | 6.3187 | 7.8706 | 61.2 | 3.1 | 24.6 |

Table 18. Results from group differences between the covert and overt naming conditions in the Motor Execution task among CWNS and CWS.
Bolded clusters indicate where CWNS > CWS.

Between Group Differences in Motor Execution.

The interaction term was used to identify voxel clusters where CWS and CWNS demonstrated different patterns of cortical activity between covert and overt naming conditions. The ANOVA results from the group by condition interaction term reflect regions of atypical speech-motor planning among CWS. Results from the ANOVA identified 11 clusters that survived the correction for multiple comparisons. These clusters are presented in Table 19.

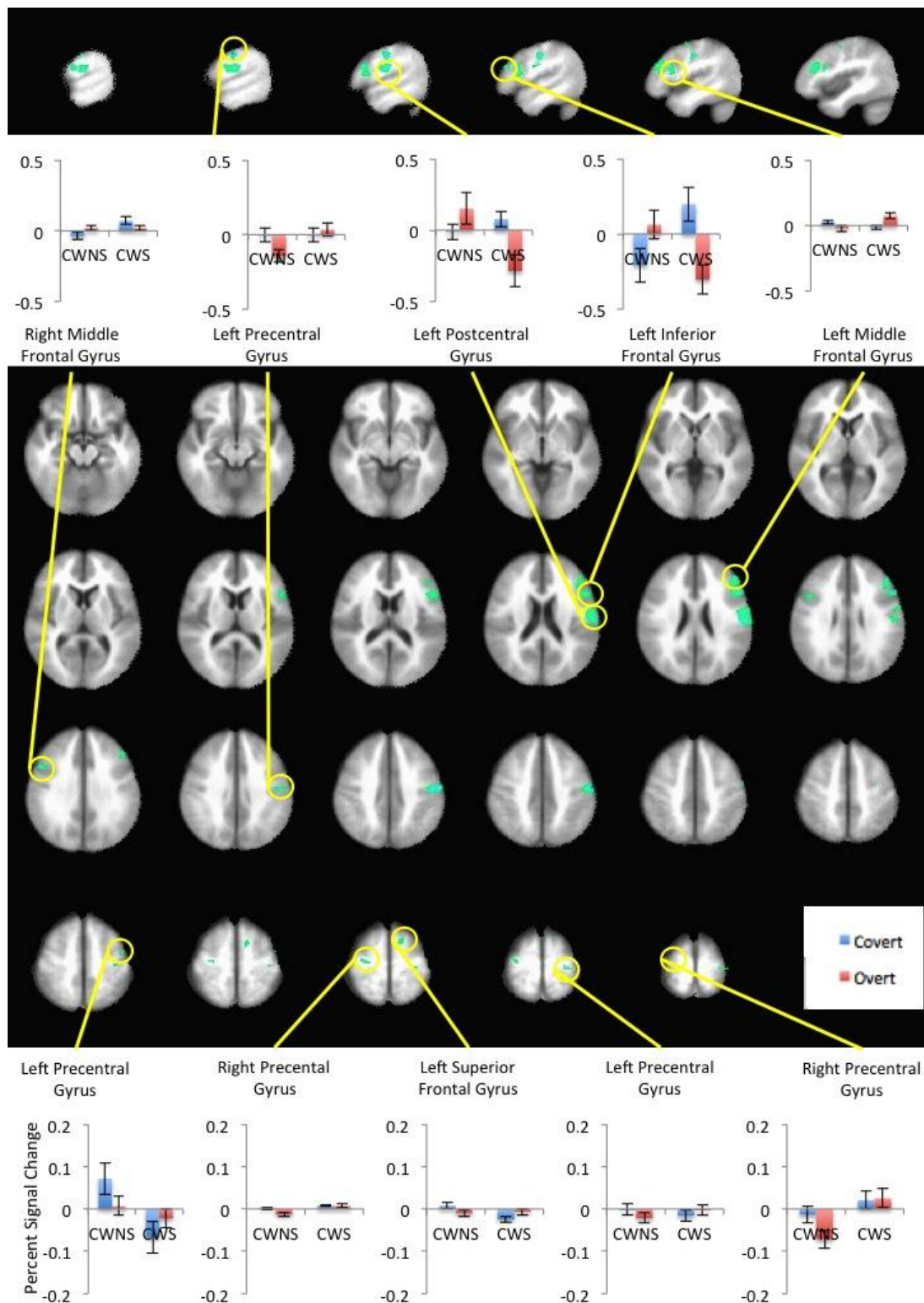


Figure 15. Clusters demonstrating a significant group effect in Motor Execution among Children. Clusters where CWS > CWNS are depicted with a circle, while clusters where AWS < AWNS are depicted with a square.

Among CWNS increased speech-motor execution was associated with increased HbO in the left inferior frontal gyrus, post central gyrus and the right middle frontal gyrus. CWS, however, demonstrated reduced HbO in the left inferior frontal gyrus, precentral gyrus and the right middle frontal gyrus. CWNS demonstrated reduced HbO in the left middle and superior frontal gyri, and bilaterally in the precentral gyrus. In those same regions, however, CWS demonstrated the opposite trend, demonstrating an increase in HbO in the left middle and superior frontal gyri and bilaterally in the precentral gyrus.

Figure 16 presents the voxel clusters that survived the correction for multiple comparisons along with bar plots depicting the HbO for covert and overt naming at each cluster.

Post hoc t-tests were completed to determine if CWS and CWNS demonstrated significantly different levels of cortical activity during each condition at each significant cluster. CWS and CWNS demonstrate significantly different levels of HbO in five clusters. During covert naming, the difference between HbO between the groups in the left superior frontal gyrus approached significance with CWS demonstrating reduced HbO than CWNS ($t_5 = 2.559$ $p = 0.051$). During overt naming relative to CWNS, CWS demonstrated reduced HbO in the left post central gyrus ($t_5 = 3.086$ $p = 0.027$) and in the inferior frontal gyrus ($t_5 = 2.561$ $p = 0.05$). Relative to CWNS, CWS demonstrated increased HbO in two clusters in the right precentral gyrus, one cluster in the dorsal premotor area ($t_5 = 2.908$ $p = 0.033$) and the second in the dorsolateral premotor area ($t_5 = 4.243$ $p = 0.008$).

Discussion.

The primary results indicate that during cortical activity associated with speech-motor execution CWS demonstrate atypical activity in the left inferior frontal gyrus relative to CWNS. During overt naming CWS demonstrated a decrease in activity relative to covert naming; whereas, CWNS demonstrated an increase in cortical activity during overt naming.

| Region | Hem. | BA | Volume (mm ³) | F _{11, 76} | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|---------------------------|---------------------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Post central Gyrus | Left | 3 | 2776 | 7.264 | 12.712 | 58 | 11.6 | 23.1 |
| Inferior Frontal Gyrus | Left | 45 | 2088 | 6.8124 | 13.951 | 50.7 | -17.1 | 20.4 |
| Middle Frontal Gyrus | Left | 46 | 1712 | 6.6126 | 11.047 | 45 | -31.9 | 24.8 |
| Precentral Gyrus | Left | 4 | 1440 | 8.9929 | 27.524 | 53.8 | 13.4 | 41 |
| Middle Frontal Gyrus | Right | 9 | 456 | 7.0051 | 12.661 | -48.9 | -14 | 30.6 |
| Precentral Gyrus | Right | 6 | 408 | 5.8831 | 8.016 | -31.5 | 15.9 | 65.4 |
| Superior Frontal Gyrus | Left | 6 | 352 | 5.6167 | 10.186 | 13.1 | -8.3 | 63.1 |
| Precentral Gyrus | Left | 4 | 328 | 6.6278 | 10.031 | 29.6 | 25.1 | 69.3 |
| Precentral Gyrus | Left | 6 | 144 | 5.5726 | 6.7888 | 44.4 | 6 | 55.6 |
| Precentral Gyrus | Left | 4 | 120 | 5.7148 | 6.7073 | 38.4 | 21.2 | 57.7 |
| Precentral Gyrus | Right | 6 | 80 | 6.0117 | 10.248 | -20.2 | 14.3 | 77 |

Table 19. Results from condition x group interaction differences between the covert and overt naming conditions in the Motor Execution task among CWNS and CWS.

This reduced activity in the left inferior frontal gyrus may reflect anatomical differences between stuttering and fluent people. Both AWS and CWS demonstrate reduced gray matter volume in the left inferior frontal gyrus (Chang, et al., 2009). Similarly, AWS demonstrate reduced white matter connectivity between left inferior frontal and pre-motor areas (Chang, et al., 2011). These anatomical differences may indicate that the structures responsible speech-motor execution in AWNS and CWNS may not be sufficient to meet the demands of speech production in AWS and CWS.

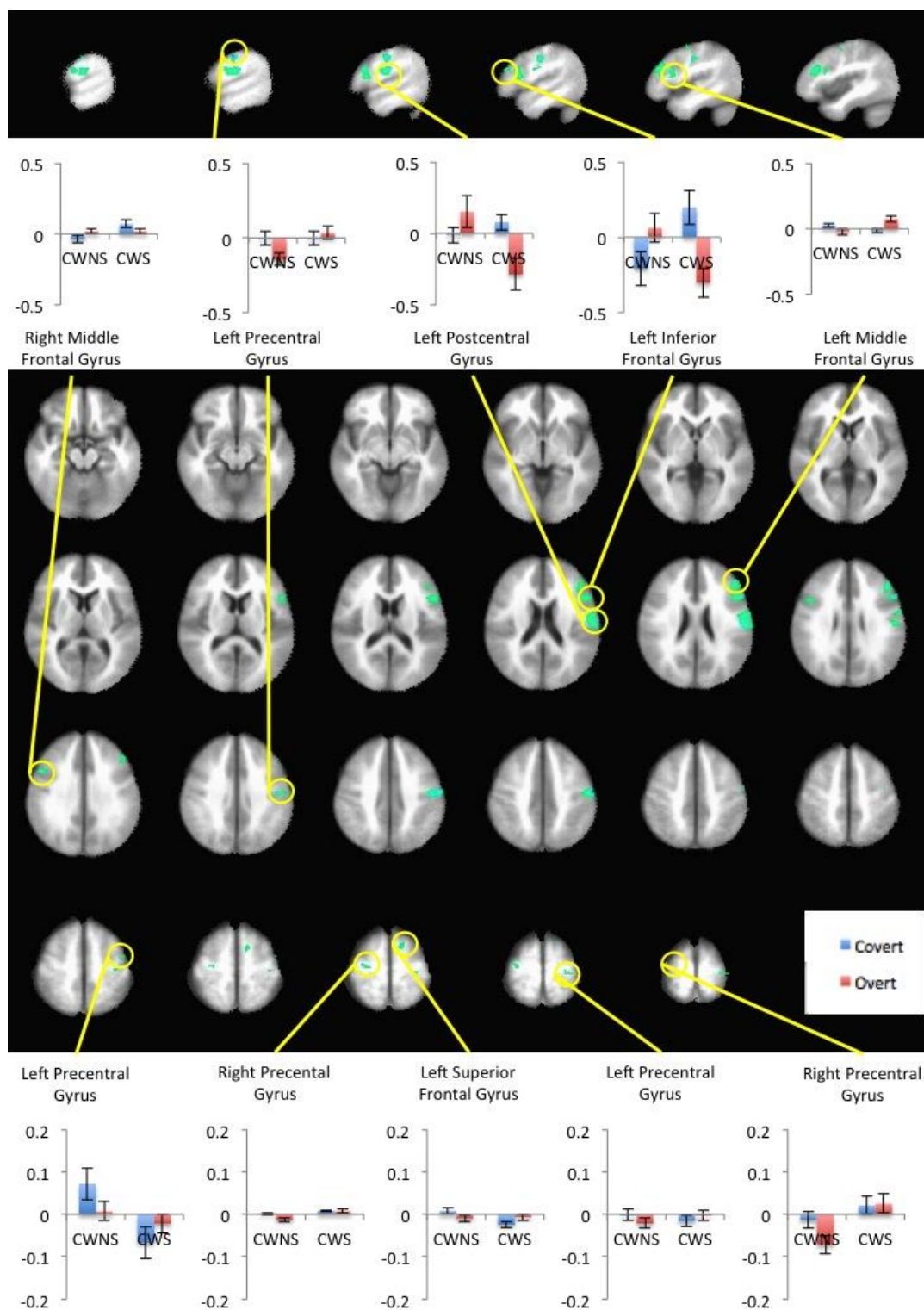


Figure 16. Clusters demonstrating significant condition x group interaction effect in Motor Execution among Children.

Activity related to covert naming is in blue while activity related to overt naming is in red. In each graph the CWNS are presented in the left columns while CWS are presented in the right. Please note that the graphs have two in order to accommodate vastly different HbO signals.

If the left inferior frontal gyrus is not capable of meeting the demand of speech production a potential source of compensation is activity in the right inferior frontal gyrus (Preibisch, Neumann, et al., 2003). Atypical right hemisphere activity was not observed during the motor-execution task. This suggests that the atypical right inferior frontal gyrus activity observed in the motor planning task is related to motor planning and not motor execution. Similarly, the absence of atypical activity in the right inferior frontal gyrus further indicates that the increased activity in the right is compensating for the increased motor planning demand and not inhibitory in nature. These results are consistent with previous reports indicate that the left inferior frontal gyrus is a primary location of atypical speech motor planning and execution (Lu, Chen et al., 2010) and that the right inferior frontal gyrus is compensating for reduced activity in the left (Preibisch, Neumann, et al., 2003).

Chapter 5: Conclusions

The purpose of this study was three fold: (1) to determine if fNIRS can replicate the findings from fMRI studies evaluating cortical activity among AWS, (2) to determine if AWS and CWS demonstrate differences in cortical activity related to speech-motor planning, execution or both, and (3) to determine if AWS and CWS demonstrate similar differences in speech motor-planning and execution. The results of the study indicate that (1) fNIRS is capable of replicating the findings from fMRI in AWS. (2) Additionally, relative to their fluent peers both AWS and CWS demonstrate differences in speech-motor planning and execution. During speech-motor planning the between-group differences observed are primarily concentrated bilaterally in the inferior and middle frontal gyri and the precentral gyrus. During motor execution, however, the clusters demonstrating significant between-group differences are more wide spread through the regions of cortex measured and include similar regions as speech-motor planning. In addition to these regions the post central gyrus and supramarginal gyrus also demonstrated atypical speech-motor execution. (3) The increased areas of atypical activity in execution relative to planning were pronounced in the CWS. Relative to AWS, CWS demonstrated substantially fewer regions demonstrating significant effects during motor planning but demonstrated slightly more regions of atypical activity during motor execution.

Differences Between Speech-Motor Planning and Execution

In both AWS and CWS the number of clusters demonstrating a between group difference was greater in motor execution compared to motor planning. This distinction was quite obvious among CWS. Although this difference in age groups

may be related to a smaller number of child participants, after taking account the process by which motor control (and specifically speech-motor control) develops, a more compelling story suggests that atypical speech-motor execution is evident earlier than atypical speech-motor planning. This would suggest a developmental influence of speech-motor execution onto speech-motor planning. This is well documented phenomenon in other motor domains of motor control (Kawato, 1999; Miall & Wolpert, 1996). Similar models have been suggested to play a role in the development of motor control related to speech and language (Kawato, 1999; Nip, Green & Marx, 2009) as well as mastication (Wilson & Green, 2009).

Considering the developmental nature of motor control atypical speech-motor execution may influence the development of speech-motor planning in ways that eventually grow to be regarded as atypical—as is potentially the case in CWS and AWS.

Development of Motor Control.

Motor control is a developmental process that is relatively complicated. The process of fine tuning motor commands to produce fluid and accurate movements involves both feedback and feedforward systems of motor control. Early in development feedforward commands are not established. Early instability is not merely a feature of insufficient muscle strength, as evidenced by the unstable movements of small children as they learn to feed themselves and manipulate small objects. Consider the development of gait; while the development of muscle tone is essential for many movements (e.g., a child must develop the leg strength to stand before attempting to walk), muscle tone is only one piece of the motor control

puzzle. During the early stages of walking small children experience failure in their gait as a result of transitioning between walking surfaces and utilizing different footwear. These are not a feature of muscle tone, but of the changes in motor movement necessary to accommodate different floors and shoes.

These failures in motor performance are essential for the development of motor control. Accurate and precise motor control is developed through an integration of both feedback and feedforward motor control systems. The development of feedforward mechanisms has been demonstrated in speech production; the DIVA model has demonstrated that speech production becomes more stable and accurate by integrating the feedback signal into the motor control process (Guenther, et al., 2006). Using computer simulations of the neural networks included in the DIVA model can develop from babbling stages to adult word production by integrating the auditory error signal (expected production – observed production) of the previous production into the next production. This process of integrating acoustic feedback culminates in a system that is able to produce adult forms of words in highly consistent and accurate ways.

In the development of motor control for movement is marked by a reduced ability to scale the direction and force of movements in various domains including force grip (Forssberg, Eliasson, Kinoshita, Johansson & Westling, 1991), reaching (Matthew & Cook, 1990), and arm movements (Thelen, 1991, 1995). The development of accuracy in motor movements integrates domain-specific feedback (e.g., proprioceptive, acoustic, visual, tactile) into the developing feedforward mechanisms to highly tune the system into a collective unit of muscles and sensory

organs that generates movements in highly accurate and precise ways. The accuracy and control of adult movements are facilitated by the integration of sensory feedback information into sensory expectations that influence upcoming movement trajectories.

The accuracy of speech production and mastication develop in similar ways. Speech production (Green et al., 2000; Nip, Green & Marx, 2009) and oromotor control for mastication (Wilson & Green, 2009) are marked by increased variability in movement and reduced speed. Over time movement variability is not only reduced, but it is reduced in specific ways. For instance, early in the development of mastication immature movements are characterized by high degrees of vertical and horizontal mandible excursion. Over the course of development the variability of horizontal excursion substantially reduces (Wilson & Green, 2009). In the case of speech production, however, there is a reduction in the vertical and horizontal jaw movement variability. However, it is not a linear reduction in variability (Nip & Green 2009). During periods characterized by vast lexical development the variability significantly increased. A greater lexicon will require a greater number of unique words requiring a greater number of unique movement trajectories. Thus as the lexicon increases the demand for feedforward control increases; however, the new and novel movements have not yet had experiences with the novel movements to provide sufficient feedback in order to develop the feedforward systems. As such the motor system appears to retreat to a more juvenile state: increased variability. The motor system again tunes itself and continues its progression towards the adult forms of words characterized by highly precise and accurate movements.

Atypical Motor Control.

The results of the DIVA model simulations and kinematic studies of speech production highlight the importance of both acoustic and proprioceptive feedback in the development of speech production. The DIVA model has demonstrated how increased reliance on acoustic feedback can result in disfluencies (Civier, et al., 2010). However, what remains unclear is what might drive a system to rely more heavily on acoustic feedback. Using current models of motor control can provide an ecologically plausible model for the development of a speech production system that relies more heavily on acoustic and proprioceptive feedback.

The development of feedforward control systems utilizes the incoming acoustic and proprioceptive feedback to develop sensory expectations for the expected movements. A motor control system that demonstrates atypical development of feedforward systems may be a system with a reduced ability to integrate proprioceptive and acoustic feedback during motor learning tasks. A barrier for motor learning may indicate that the incoming feedback is either inaccurate or incomplete. If the incoming feedback is inaccurate or incomplete the resulting feedforward systems will lack specificity. Feedforward systems that lack specificity may result in a movement system that generates more variable movements. Fundamental and pervasive findings from kinematic studies in stuttering demonstrate that AWS demonstrate reduced motor learning capabilities both immediately and long term (Max & Caruso, 1997) and increased variability in perceptually fluent speech movements (Kleinow & Smith, 2000; Smith & Kleinow, 2000). Similarly, feedforward systems that lack specificity may be prone to errors in

speech production, particularly during complex speech tasks, like phonologically complex nonwords. CWS demonstrate an increased comorbidity of phonological disorders (Louko, 1995; Louko, Edwards & Conture, 1990; Wolk et al., 2000). Taken together it is plausible that the motor impairment underlying stuttering is driven by a motor control system that demonstrates reduced integration of incoming acoustic and proprioceptive feedback into the developing feedforward systems.

Neurophysiology of Atypical Motor Control in Stuttering.

According to the DIVA model the left inferior frontal gyrus is an essential component of the feedforward systems—it contains the plan for articulatory gestures involved in the production of speech sounds. In the DIVA model commands from the left inferior frontal gyrus are communicated to the precentral gyrus, which contains the articulator position and velocity maps—the current state of articulatory movements. As such the articulator position and velocity will integrate plans from the speech sound map and scale them appropriately given the current state of the articulators, after accounting for the inputs from the right inferior frontal gyrus.

The right inferior frontal gyrus is partially responsible for the feedback control map, as such it is an essential player in the feedback control circuitry. The feedback control map receives inputs from the somatosensory error map (post central gyrus and supramarginal gyrus) as well as the auditory error map (Heschl's gyrus, posterior aspect of the superior temporal gyrus). The feedback control map will integrate the information from the auditory and somatosensory error signals to generate a correction signal. The feedback control map then sends its inputs to the

precentral gyrus to be integrated with the speech sound map (left inferior frontal gyrus) and the articulator velocity and position maps (precentral gyrus). The combined result of all three of these inputs are motor commands to the articulatory musculature.

The contraction of these muscles is perceived as two input sources—proprioception of the current state of the articulatory system and the acoustics of the sound pressure wave generated by oral structures. These inputs enter the speech-motor control circuitry and the process continues with both feedforward and feedback control systems influencing the process of ongoing speech production.

During at least one position in this process the speech production of AWS and CWS is disrupted. The source of atypical neurophysiology of stuttering has been studied for decades; however, few studies have examined functional brain activity among both AWS and CWS (Sato, et al., 2011). The current findings confirm several of the findings from fMRI, but also present a new interpretation of the differences in speech motor control between stuttering and fluent speakers.

Motor execution is characterized by substantially more clusters demonstrating atypical activity in AWS and CWS. The effect is mirrored in HbR (see Appendix C). Differences in motor control appear to be more pervasive in speech-motor execution than speech-motor planning. This effect is pronounced in CWS. The difference in the number of clusters demonstrating significant differences in speech-motor planning was dramatically reduced compared to those observed in speech-motor execution.

Among AWS speech-motor planning and execution was associated with atypical activity in clusters in both hemispheres; specifically, bilaterally in the inferior frontal gyri and the precentral gyrus and in the right middle frontal gyrus. AWS demonstrated reduced activity in the left inferior frontal gyrus, which may reflect weaker representations of the speech sound maps in the feedforward systems. Several studies have suggested that increased activity in the right inferior frontal gyrus is related to compensatory strategies for decreased speech-motor planning in the left (Lu, Chen, et al., 2010; Preibisch, Neumann, et al., 2003). Lu, Chen, et al., suggested that the right inferior frontal gyrus was likely to be more active in speech-motor planning than execution because of the inhibitory role of the right inferior frontal gyrus on speech acts (Chevier, Noseworth & Schachar., 2007). Using a similar strategy, Preibisch, Neumann, et al., determined that the right inferior frontal gyrus was demonstrating a compensatory role because a positive correlation between stuttering severity and activity in the right inferior frontal gyrus was not present. However, their results also indicate that the right inferior frontal gyrus was significantly more active in AWS during tasks that required no movement. As such, it is difficult to determine why increased activity in the right inferior frontal gyrus would be related to speech production generally let alone stuttering severity.

However, a more compelling result may be reached by considering DIVA—increased activity in the right hemisphere inferior frontal gyrus may be related to an increased error signal due to inefficient feedforward systems. This would suggest that the primary dysfunction in the development of feedforward mechanisms lies not in the detection of errors but the integration of errors into the feedforward

systems. In DIVA one of the primary ways the feedforward systems develop is through the simulation of cerebellar inputs in to the feedforward systems in the precentral gyrus (Guenther et al., 2006). The cerebellum is highly connected with the motor system, with afferent connections from the premotor cortical areas (Schmahann & Pandya, 1997) and efferent connections to the precentral gyrus (Middleton & Strick, 1997). The cerebellum has been implicated to contribute to stuttering, and AWS have demonstrated atypical activity in the cerebellum during speech production (De Nil, Kroll & Houle, 2001). Taken together, the decreased activity in the left hemisphere inferior frontal gyrus, increased activity in the right inferior frontal gyrus and atypical activity in the cerebellum may more accurately reflect disfunction in the development of feedforward systems of speech-motor control.

Inferior and Middle Frontal Gyri.

Previous reports have theorized that the left inferior frontal gyrus is a primary source of atypical speech-motor planning and execution in AWS (Lu, Chen, et al., 2010). The current study has confirmed the role of the left and right inferior frontal gyrus as a potential source of atypical speech-motor control. Additionally, CWS demonstrate the same atypical activity in the bilateral inferior frontal gyri as AWS indicating that the atypical neurocorrelates of speech-motor planning and production have emerged sometime before the school-age years.

Results from the current study demonstrate that among both AWNS and CWNS speech-motor planning and execution was associated with increased activity in the left inferior frontal gyrus. However, among AWS and CWS the role of the left

inferior frontal gyrus in speech production is more complicated. During motor planning, AWS and CWS demonstrated increased activity in the right inferior frontal gyrus. This is consistent with previous reports of cortical activity during speech production. Increased right inferior frontal gyrus has been thought to play a compensatory role. The results of the current study are consistent with this hypothesis: atypical right inferior frontal gyrus activity was associated with speech-motor planning and not speech-motor execution. This confirms the hypothesis.

During speech-motor execution, AWS and CWS demonstrated atypical activity in the left inferior frontal gyrus relative to AWNS and CWNS. Given previous findings that AWS and CWS demonstrate reduced gray matter volume in the left inferior frontal gyrus (Chang et al., 2009) and reduced white-matter connectivity between left inferior frontal and pre-motor regions, the results of the current study are consistent with previous reports indicating that stuttering is associated with disruption in the left inferior frontal gyrus (Lu, Chen et al., 2010; Preibisch, Neumann, et al., 2003). Taken together the results of the current study indicate that in both AWS and CWS demonstrate atypical cortical activity in the left and right inferior frontal gyri in predictable patterns: atypical activity on the left is associated with inefficient motor execution while atypical activity on the right is associated with compensatory motor planning.

Previous reports have suggested that increased right hemisphere activity is a risk factor for the development of stuttering. However, recent MEG reports indicating the preschool CWS do not demonstrate atypical brain activity from CWNS during a picture-naming task (Sowden et al., 2014). While school age children

demonstrate reduced gray matter volume bilaterally in the inferior frontal gyrus (Chang, et al., 2009) they do not demonstrate increased volume of the corpus callosum like their adults peers (Choo, et al., 2011, Choo, et al., 2012) indicating that the connections between the hemispheres are strengthened overtime. Taken together the results from the current study indicate that stuttering may result from reduced specialization of the left hemisphere for speech production. Both AWS and school age CWS demonstrate atypical cortical activity associated with speech motor planning and execution in the inferior frontal gyrus. Both AWS and school age CWS demonstrate atypical cortical activity in the right middle frontal gyrus in regions associated with prosody. Right hemisphere inferior frontal gyrus activity may be necessary due to reduced gray matter volume in the left hemisphere; as a result the interhemispheric connections between the frontal lobes remain greater than in AWNS and CWNS.

Superior Temporal Gyrus.

Atypical activity in the superior temporal gyri has been well documented in the literature and is among the most robust findings. AWS have demonstrated deactivations in the superior temporal gyrus bilaterally (Brown, Ingham, Ingham, Laird & Fox, 2005) others demonstrated reductions in only the left superior temporal gyrus (Fox, et al., 1996), As such, the superior temporal gyrus was expected to be a substantial source of between group differences in the current study. These differences have been implicated to contribute to articulatory planning (Craig-McQuiade, Akarm, Zrinzo & Tripoliti, 2014). As such deactivations in the left superior temporal gyrus were expected during the motor planning task. The left

superior temporal gyrus did demonstrated increased activity during the different syllable nonwords task, however, the current study demonstrated intriguing results—AWS demonstrated increased activity in the left superior temporal gyrus relative to AWNS. This may indicate that that the current task isolated the functional activity of the superior temporal gyrus more accurately than previous studies. Also, the function of the superior temporal gyrus is thought to reflect different aspects of processing auditory feedback. Few of the previous reports have attempted to parse speech-motor planning from execution. Additionally, many of the studies measured brain activity during speech tasks that were longer than the current study (e.g., reading sentences). The deactivations observed in previous reports may be a feature of ongoing speech production.

Differences in the activity in the superior temporal gyrus were only observed in adults. The lack of significant results in children suggests that deactivations observed in previous studies may be the result of experience with stuttering. However, it must also be noted that the lack of findings may also have been due to a relatively small sample size.

Perceptually Fluent Speech

There is a long standing tradition of describing only the differences observed in the perceptually fluent speech of both AWS and CWS. This tradition extends to acoustic, kinematic and electromyographic studies of the timing relationships in acoustic events and articulator movement gestures. The rationale for excluding disfluent speech from these analyses is to determine if disfluent speech represents a fundamentally different kind of movement gesture (and resulting acoustic events)

or if disfluencies reflect a difference in the degree of motor impairment. Said differently, the study of perceptually fluent speech is done in an attempt to determine if there is evidence of a motor impairment that does not exceed a threshold to trigger disfluencies.

The same rationale can be used for the examination of cortical activity associated with speech-motor planning and execution. From previous acoustic, kinematic and electromyographic studies it is well established that AWS and CWS demonstrate subtle differences in the timing of acoustic events, movement of articulators and degree of muscle contraction during perceptually fluent speech. As such these studies indicate that the effects of stuttering are present even when the behavior of stuttering is absent. These differences in the movement of oral and laryngeal structures are driven by cortical commands and influenced by subcortical tuning of cortical commands. As such, excluding disfluent trials allows the examination of a neural network for speech production that is successfully achieving its goal (fluent speech production), albeit through differences in both the regions involved in the neural networks and the degree of activity observed in these regions.

Differences observed in the neural networks of perceptually fluent speech have been used to determine changes in cortical and subcortical activity after a period of intensive therapy. One notable change is observed in the inferior frontal gyrus. After an intensive course of “fluency-shaping” therapy, AWS demonstrated increased activity in the left and decreased activity in the right—that is after therapy, functional activity related to speech production in AWS appeared to

become more consistent with that of the AWNS (Neumann, et al., 2003). While these results are striking, it is unclear if these differences result from reorganization of neural networks to promote fluent speech production or a reflection of the changes in the physiology of speech production resulting from fluency-shaping therapy.

This is not to suggest that disfluent trials should not be studied. Few studies have examined activity related to stuttered speech production. An early study unsuccessfully attempted to simulate the atypical patterns of functional brain activity observed in AWS by asking AWNS to produce purposeful stuttering (De Nil, et al., 2008). However, few studies have examined cortical activity associated with stuttered speech production. This should be encouraged. At present there are more than likely many laboratories with data reflecting cortical activity related to stuttered speech production. Differences in the cortical activity between stuttered and fluent speech production are essential for determining if stuttered speech production reflects a difference in the degree of an ongoing motor impairment or a fundamentally different method of speech production.

Limitations

Finding a sufficient number of participants is a common problem for many stuttering researchers. In the case of the current study finding children who stutter, particularly preschool children who stutter, was quite difficult. As such it is possible that there were ROIs that failed to reach significance because of a lack of sufficient power.

The Motor Planning task was designed to so that the repeated syllable nonwords and the different syllable nonwords differed only in the number of

syllables required to be planned and executed. However, they differed in syllabic stress as well. The repeated syllable nonwords were produced with equal stress on each syllable, whereas, the different syllable nonwords had a syllabic stress pattern that was more consistent with connected speech. As such, the cortical activity related to motor planning is confounded with activity related to prosody.

Future Research

The current study has identified that CWS demonstrate atypical cortical activity related to speech motor planning and execution. The science of the neurophysiology of stuttering continues to require investigations of speech motor planning and execution in preschool children near the onset of stuttering. The best investigations would be longitudinal studies of developmental changes in the neurophysiology of stuttering.

Statistical comparison of cortical activity between adults and children was not possible because of differences in the brain atlas used as reference for each age group. Future research should attempt to rectify the differences in atlases to allow the direct comparison between adults and children.

This study has demonstrated evidence describing potential dysfunction in the left inferior frontal gyrus. This should continue to be explored. Future research could examine cortical activity during stuttered speech in order to determine if activity in the left inferior frontal gyrus is suppressed relative to activity during perceptually fluent speech. Studies should also consider examining cortical activity of speech production during tasks with unreliable feedback—such examples could

be the mechanical perturbation of the jaw (e.g., Bauer, Jancke & Kalveram 1995) or under delayed auditory feedback (Cai, Ghosh, Guenther & Perkell, 2012).

To further investigate the role of speech-motor planning among AWS, cortical activity during repeated and different syllable nonwords with identical prosodic structure should be considered.

Appendix A

Communication History Questionnaire: Adults

Stuttering Research Lab
Department of Communication Sciences and Disorders
University of Iowa
Participant History—Adult

Research # _____ Gender _____
Address _____ Date _____
City _____ DOB _____
State _____ Zip _____
Contact Phone _____
Email _____
Occupation _____
Highest level of education _____

Questions

1. Have you had any serious medical health problems or conditions since birth (e.g., pneumonia, RSV, hear defects, epilepsy, asthma, diabetes, head injuries)? If yes please specify dates and if hospitalization was required.
2. Are you on any medication now? If yes, please specify.
3. Have you ever had a diagnosis behavioral or psychological problem (ADHD, ADD, depression, behavior disorders).
 - a. Yes ☐ No ☐
 - b. If yes please provide specifics including treatments, if any.
4. Have you ever had a vision screening?
 - a. Yes ☐ No ☐
 - b. If no, do you have any concerns about your vision?
5. Aside from stuttering, have you ever had any speech/language or hearing problem?
6. Have you ever received any treatment for speech, language and hearing disorders? If yes please provide details.
7. How old (in years) were you when you first began to stutter?
8. Did a certified speech-language pathologist make a diagnosis of stuttering?

9. Have you ever received speech therapy for stuttering?
- If yes please provide:
 - Date treatment began (month, year)
 - Date treatment ended (if applicable)
 - Time (in hours) per week in treatment
10. Please check any of the following behaviors that are typical of your speech
- Repetitions of parts of words: b-b-b-b-blue
 - Yes ☐ No ☐
 - Repetitions of short words: and-and-and-and
 - Yes ☐ No ☐
 - Prolonging sounds: mmmmmmmmmommy, oooooooooopen
 - Yes ☐ No ☐
 - Blocks, "couldn't get the sound out": c-----at, -----ball
 - Yes ☐ No ☐
 - Lip, jaw, eye, facial, body tension and/or movements
 - Yes ☐ No ☐
11. How often do you stutter? (circle one)
- Frequently
 Sometimes
 Rarely
 Never, no concern
12. Rate the severity of your stuttering.
- | | | | | | | |
|--------|---|------|---|----------|---|--------|
| Normal | | Mild | | Moderate | | Severe |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 7 |
13. Has anyone else in the family ever had a speech or language problem?
- Yes ☐ No ☐
 - If yes, who and what kind of problems

Communication History Questionnaire: Children

Stuttering Research Lab
Department of Communication Sciences and Disorders
University of Iowa
Participant History—Child

Research # _____ Gender _____
Address _____ Date _____
City _____ DOB _____
State _____ Zip _____
Contact Phone _____
Email _____
Parents' Occupation _____
Parents' Highest level of education _____
Other children in family (age & gender) _____

Questions

1. Has your child had any serious medical health problems or conditions since birth (e.g., pneumonia, RSV, hear defects, epilepsy, asthma, diabetes, head injuries)? If yes please specify dates and if hospitalization was required.
2. Is your child on any medication now? If yes, please specify.
3. Has your child ever had a diagnosis behavioral or psychological problem (ADHD, ADD, depression, behavior disorders)?
 - a. Yes ☐ No ☐
 - b. If yes please provide specifics including treatments, if any.
4. Has your child ever had a vision screening?
 - a. Yes ☐ No ☐
 - b. If yes, did your child have normal vision?
 - i. Yes ☐ No ☐
 - ii. If no, please note if your child wears glasses or contacts, or if you have any concerns regarding your child's vision.
5. Aside from stuttering, has your child ever had any speech/language or hearing problem?
6. Has your child ever received any treatment for speech, language and hearing disorders?
 - a. Yes ☐ No ☐

- b. If yes please provide details.
7. How old was your child when he or she first began to stutter?
8. Did a certified speech-language pathologist make a diagnosis of stuttering?
- a. Yes ☐ No ☐
9. Has your child ever received speech therapy for stuttering?
- a. If yes please provide:
- i. Date treatment began (month, year)
- ii. Date treatment ended (if applicable)
- iii. Time (in hours) per week in treatment
10. Please check any of the following behaviors that are typical of your child's speech
- a. Repetitions of parts of words: b-b-b-b-blue
- i. Yes ☐ No ☐
- b. Repetitions of short words: and-and-and-and
- i. Yes ☐ No ☐
- c. Prolonging sounds: mmmmmmmmmommy, oooooooooopen
- i. Yes ☐ No ☐
- d. Blocks, "couldn't get the sound out": c-----at, -----ball
- i. Yes ☐ No ☐
- e. Lip, jaw, eye, facial, body tension and/or movements
- i. Yes ☐ No ☐
11. How often does your child stutter? (circle one)
- Frequently
- Sometimes
- Rarely
- Never, no concern
12. Rate the severity of your child's very early stuttering.
- | | | | |
|--------|--------|----------|--------|
| Normal | Mild | Moderate | Severe |
| 0 1 | 2 3 | 4 5 | 6 7 |
13. Rate the severity of your child's current stuttering.
- | | | | |
|--------|--------|----------|--------|
| Normal | Mild | Moderate | Severe |
| 0 1 | 2 3 | 4 5 | 6 7 |
14. Has anyone else in the family ever had a speech or language problem?
- a. Yes ☐ No ☐
- b. If yes, who and what kind of problem

Appendix B

The process of constructing the cap for fNIRS data collection was a multi-step process that involved identifying ROIs, designing and testing the probe geometry and scaling the geometry to place on caps of different circumferences.

ROI Selection

The process of selecting regions of interest (ROI) involved a process developed by the Child Imaging Laboratory in Developmental Science (ChILDS) at the University of Iowa's Development from Learning to Theory and Application (DeLTA) Center (Wijeakumar et al., 2015). There are six steps in this process. (1) Estimate particular regions of interest in the brain as determined by reports of fMRI studies examining brain activity during speech production and language processing in adults who stutter (AWS) relative to adults who do not stutter (AWNS). To be included in further analysis reports had to be published in a peer-reviewed journal, report coordinates in either Talaraich or Montreal Neurological Institute (MNI) space and compare brain activity between AWS and AWNS during speech production or language processing tasks. The publications selected represented five separate laboratories from across the globe including three in North America, one in Asia and one in Europe (Chang et al., 2009; Lu et al., 2009; Lu, Peng, et al., 2010; Neumann et al., 2003; Preibisch, Neumann, et al., 2003; K. E. Watkins et al., 2008). Two additional publications were added because our procedure included a finger tapping task and a resting state task (Sadato et al., 1996; Xuan et al., 2012). (2) All coordinates demonstrating significant brain activity both within and between

groups were selected. If Talairach coordinates were reported they were converted to MNI coordinates using GingerAle© (BrainMap) using the Statistical Parametric Mapping (SPM) procedure. A customized MatLab script calculated the Euclidean distance between all pairs of coordinates.

(3) Coordinate pairs were collapsed into clusters if at least two pairs from at least two publications were no more than one centimeter apart. (4) This process resulted in 19 ROIs including seven bilateral ROIs and five unilateral ROIs. Bilateral ROIs included: Inferior and Middle frontal gyri, supplementary motor area, precentral gyrus, superior temporal gyrus, insula and inferior parietal lobule. Unilateral ROIs included: right superior frontal gyrus, left thalamus, right putamen, right culmen of cerebellum and left cingulate.

(5) Confirmation of individual coordinates in each coordinate cluster was achieved by visual inspection of coordinates plotted in ANFI brain space. Three coordinates did not match the ANFI anatomical label, and were removed from the dataset. (6) A second MatLab © procedure generated regions of interest (ROI) by averaging of all coordinates in a coordinate clusters. A three-dimensional model of all ROIs was generated by MatLab and viewed in Slicer ©. Given that fNIRS is only capable of measuring cortical activity all subcortical ROIs were removed. This resulted in a list of 13 ROIs: seven bilateral ROIs and one unilateral ROI. The bilateral counterparts of the unilateral ROI was added as a 14th ROI generating a total of fourteen ROIs divided into seven hemispheric pairs.

Optode Geometry Site Selection

The probe geometry is closely related to the 10-20 EEG coordinate system. Of critical importance to imaging the developing brain using fNIRS is a probe geometry that scales with developing head circumference. fNIRS studies use a source-detector distance of 3cm in adults and children (Sato et al., 2012). Given the difference in head circumference (and by proxy brain circumference) a 3cm source-detector distance will gather information from a wider array of cortical structures in children compared to adults. Therefore, a more precise method of determining source-detector distance is necessary.

The standard source-detector distance in infant fNIRS studies is 1.9 cm. Typical EEG caps used for infants have a 36cm circumference, thus in a 36 cm circumference cap optodes are 1.9cm apart. Scaling up to a 60cm circumference cap with a 3.0cm optode distance, every 2cm increase in head circumference results in a 1mm increase in optode distance. This method allows a relative geometry that will be anatomically consistent across multiple populations of various ages.

Verification Simulations.

The probe geometry was initially started by estimated a distribution of light sources and detectors that was estimated to cover the ROIs. The optode geometry was designed adhering to 10-20 system coordinates. The three dimensional position of light sources and detectors was digitized relative to the nasion, inion, CZ, and bilateral auricular points (A1, A2). Monte Carlo simulations were run comparing the position of sources and detectors relative to ROIs. After visually inspecting the results from Monte Carlo simulations, adjustments were made in the probe

geometry to increase the best fit for all ROIs. The final probe geometry is as follows. The geometry is symmetrical, for the purposes of this document the description will be based on right hemisphere 10-20 locations. The left hemisphere is the mirror of the right hemisphere.

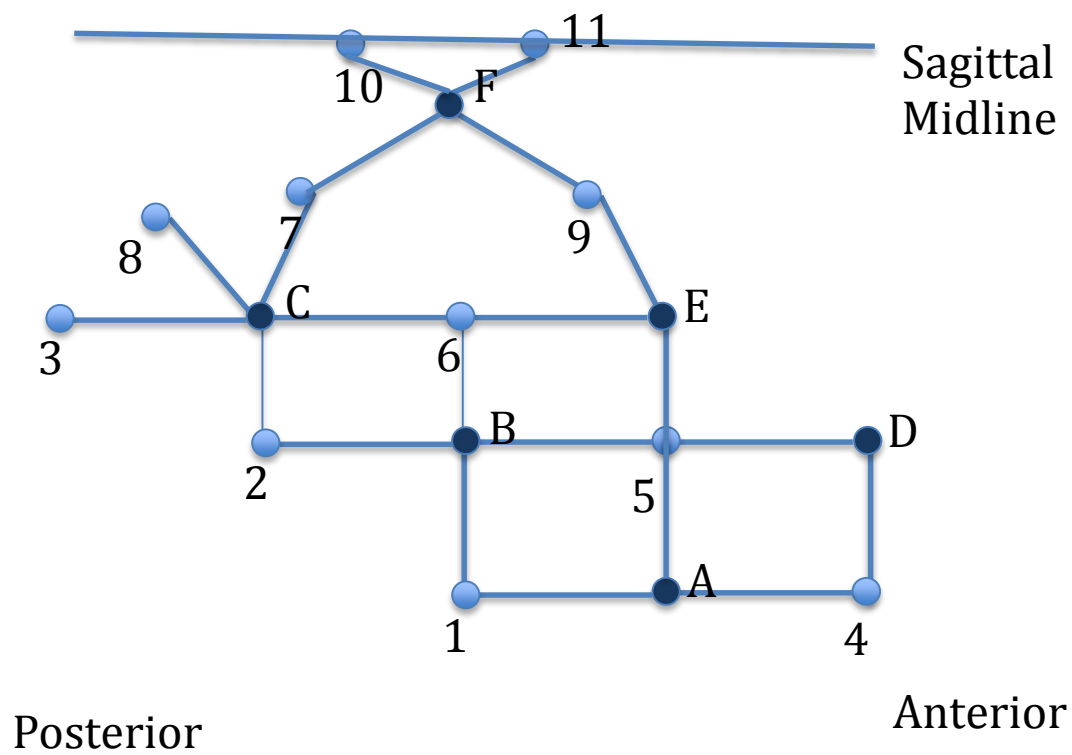
Cap Design

Beginning with anchor points at F8, T8 and P4, the best fit required rotating the pitch of the optode grid anteriorly. We decreased the slope of the grid by elevating T8 and P4 by 20% of the 10-20 system distance. Thus, by taking a drafting compass set to the F8-T8 distance we moved the anchor point at T8 20% of the F8-T8 distance superiorly. For the P4 anchor point, the drafting compass was set to 20% of the P4-CZ distance and a circle around P4 was drawn. Of fundamental importance was ensuring the relative distance between optodes remained the same across caps, thus optodes in the grid needed to be the same relative distance as the original. The P4 anchor point was defined as the intersection of the 20% circle around P4 and the relative optode distance.

Optode Geometry.

Figure 1 displays a graphic representation of probe geometry for the right hemisphere (not to scale). Dark circles are light sources (lettered A-F) and lighter circles are light detectors (numbered 1-6). There were six sources and nine detectors placed on each hemisphere with two detectors on the sagittal midline. Three detectors were placed on the anchor points (detector 4 at F8, detector 1 at the approximated T8 and detector 3 at the approximated P4). Detector 2 was placed at the midpoint of the T8-P4 line. Source A was placed at the midpoint of the T8-F8

line. Using a drafting compass set to a relative distance determined by cap circumference (matching the relative change in 10-20 distance) sources were defined by the radial intersection of the compass rotations around adjacent detectors. Detectors were defined by the radial intersection of compass rotations around adjacent sources. Thus, source B was the radial intersection of circles centered at detectors 1 and 2. Detector 5 was the radial intersection of circles centered on source A and source B. Sources B and C and detectors 5 and 6 were defined using this method. Detector 7 was defined as the point where the radial distance of a circle centered around source C intersected a line between CZ and source C. Detector 8 was defined as the point where the radial distance of a circle centered around source C intersected a line between PZ and source C. Detector 9 was defined by the point where the radial distance of a circle centered around source E intersected a line between CZ and source E. Source F was defined by the radial intersection of circles centered around sources 7 and 9. Detectors 10 and 11 were defined by the radial intersection of a circle centered on source F at the point where it crosses the midline anteriorly and posteriorly. Two detectors were placed directly adjacent to two sources in order to account for changes in tissues oximetry. These short source-detector pairs (not shown in figure 1) are adjacent to sources B and F.



Appendix C

Picture Identification Stimuli

| Overt Naming | Covert Naming | Foil |
|--------------|---------------|------|
| arm | arm | |
| banana | butterfly | * |
| basketball | basketball | |
| bed | ball | |
| boat | boat | |
| broccoli | broccoli | |
| bus | bus | |
| button | button | |
| camera | camera | |
| car | car | |
| cat | cat | |
| celery | celery | |
| cloud | hand | * |
| cookie | carrot | |
| couch | couch | |
| cow | cow | |
| cup | cup | |
| dinosaur | dinosaur | |
| dragonfly | octopus | * |
| duck | duck | |
| elephant | kangaroo | * |
| eye | eye | |
| finger | giraffe | * |
| fly | fly | |
| fork | fork | |
| grasshopper | grasshopper | |
| hamburger | hamburger | |
| horse | glove | * |
| house | house | |
| ladybug | ladybug | |
| moon | moon | |
| mouth | mouth | |
| pants | hat | * |
| potato | potato | |
| shoe | shoe | |
| shovel | shovel | |
| socks | lamp | * |
| table | table | |
| tomato | spaghetti | * |

turtle
umbrella

spider
triangle

*
*

Nonword Repetition Stimuli

| Same Syllable | Different Syllable |
|----------------------|--------------------|
| nauk nauk nauk | baseri |
| trod trod trod | grassbrellna |
| mump mump mump | stragensaur |
| soove soove soove | spinoball |
| fark fark fark | hambearfly |
| clus clus clus | ditabug |
| oom oom oom | poapus |
| huut huut huut | kangmaroo |
| horl horl horl | octager |
| florch florch florch | camgato |
| haith haith haith | bahadi |
| bot bot bot | betoper |
| laints laints laints | eldia |
| kade kade kade | dragegel |
| hote hote hote | laybera |
| bahs bahs bahs | camangfly |
| glau glau glau | toketo |
| fas fas fas | triterphant |
| koon koon koon | umnalope |
| kund kund kund | Babeli |

Appendix D

Listed below are tables documenting the analysis on deoxygenated hemoglobin. The tables below present clusters that survived the correction for family wise correction for multiple comparisons.

Motor Planning: Adults

Within-Subjects

| Region | Hem | BA | Volume (mm3) | F 10, 279 | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|--------------|-----------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Middle Frontal Gyrus | Left | 46 | 2416 | 6.6079 | 0.1021 | 48.7 | -30.7 | 24.6 |
| Post central Gyrus | Left | 3 | 1096 | 4.6866 | 0.0261 | 25.4 | 31.3 | 69.8 |
| Inferior Frontal Gyrus | Right | 45 | 712 | 5.4697 | 0.1005 | -56 | -16.9 | 21.9 |
| Middle Frontal Gyrus | Left | 9 | 672 | 5.6164 | 0.1139 | 48.8 | -8.8 | 36 |
| Medial Frontal Gyrus | Left | 6 | 216 | 4.6322 | 0.0527 | 6.9 | 21.7 | 73.3 |
| Precentral Gyrus | Left | 4 | 160 | 4.5572 | 0.0458 | 62.9 | 3.4 | 15.3 |
| Post central Gyrus | Right | 2 | 120 | 4.6863 | 0.0996 | -60.1 | 25.6 | 43.6 |
| Precentral Gyrus | Left | 4 | 120 | 4.8964 | 0.1098 | 37.4 | 20.8 | 59 |
| Paracentral Lobule | Left | 6 | 72 | 4.478 | 0.0903 | 9.2 | 15.6 | 81.5 |
| Middle Frontal Gyrus | Left | 6 | 64 | 4.9252 | 0.1707 | 36.9 | 3.5 | 49.5 |

Motor Planning

| Region | Hem | BA | Volume (mm3) | F6, 167 | SEM | Talarach Coordinates (RAI) | | |
|-------------------------|-------|----|--------------|---------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Superior Temporal Gyrus | Right | 22 | 1216 | 4.6248 | 0.0214 | -61.8 | 12.5 | 3.5 |
| Superior Frontal Gyrus | Left | 6 | 464 | 5.1477 | 0.0868 | 15.5 | 5.8 | 73.3 |
| Middle Frontal Gyrus | Right | 9 | 376 | 4.8058 | 0.0695 | -56.8 | -7 | 34.2 |
| Middle Frontal Gyrus | Left | 46 | 64 | 4.8399 | 0.3211 | 49.3 | -36.2 | 27.7 |
| Precuneus | Left | 4a | 64 | 5.6759 | 0.3979 | 12 | 37.9 | 81.1 |
| Paracentral Lobule | Left | 3 | 56 | 5.1684 | 0.2853 | 10 | 36.4 | 74.4 |

Between Subjects Differences in Motor Planning

| Region | Hem | BA | Volume (mm3) | F4, 111 | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|--------------|---------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Superior Frontal Gyrus | Left | 6 | 64 | 4.4813 | 0.0527 | 25.2 | 8 | 65.2 |
| Superior Frontal Gyrus | Right | 6 | 56 | 4.7849 | 0.1349 | -22.3 | -16.8 | 64.9 |
| Middle Frontal Gyrus | Left | 6 | 48 | 4.4863 | 0.0751 | 22.9 | 10 | 61 |
| Superior Frontal Gyrus | Right | 6 | 40 | 4.5066 | 0.0847 | -21.6 | 14 | 72.4 |

Motor Planning: Children Within-Subjects

| Region | Hem | BA | Volume (mm3) | F8, 87 | SEM | Talarach Coordinates (RAI) | | |
|--------------------------|-------|----|-----------------|--------|--------|----------------------------|------|------|
| | | | | | | x | y | z |
| Superior Frontal Gyrus | Left | 6 | 2416 | 7.0516 | 0.0759 | 17.5 | 0.4 | 65.4 |
| Middle Frontal Gyrus | Right | 6 | 976 | 5.6271 | 0.0403 | -33.6 | -9.6 | 48.8 |
| Inferior Parietal Lobule | Right | 40 | 576 | 7.43 | 0.2455 | -53.8 | 30.7 | 49.6 |
| Precentral Gyrus | Right | 4 | 240 | 5.6453 | 0.0973 | -47.2 | 13.8 | 49 |
| Inferior Parietal Lobule | Right | 40 | 208 | 5.7145 | 0.1206 | -46.1 | 46.8 | 59.5 |
| Post central Gyrus | Right | 2 | 176 | 6.1614 | 0.1958 | -33 | 37 | 67.8 |
| Precentral Gyrus | Right | 6 | 112 | 5.6956 | 0.1364 | -32.6 | 11.7 | 65.9 |
| Precentral Gyrus | Right | 6 | 48 | 5.567 | 0.1348 | -27 | 14 | 63 |

Motor Planning

| Region | Hem | BA | Volume (mm3) | F9, 98 | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|-----------------|--------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Frontal Gyrus | Right | 44 | 880 | 6.325 | 0.1143 | -45.5 | -6.1 | 30.1 |
| Precentral Gyrus | Right | 4 | 840 | 6.2552 | 0.1129 | -43 | 11.9 | 52.8 |
| Inferior Frontal Gyrus | Right | 45 | 616 | 7.0496 | 0.1612 | -45.9 | -28.2 | 19.5 |
| SMA | Right | 6 | 592 | 6.5599 | 0.1516 | -6.2 | -2.9 | 69.6 |
| Middle Frontal Gyrus | Right | 46 | 328 | 6.8375 | 0.2082 | 48 | -23.9 | 33.8 |
| Superior Frontal Gyrus | Right | 6 | 272 | 5.3038 | 0.0462 | -35.1 | 24.3 | 61 |
| Middle Frontal Gyrus | Left | 9 | 192 | 5.8329 | 0.1405 | -29.9 | 20 | 71 |
| Precentral Gyrus | right | 4 | 128 | 5.6974 | 0.1509 | -52.1 | 33.7 | 44.3 |
| Precentral Gyrus | right | 4 | 96 | 5.2974 | 0.0943 | -58.3 | 23.9 | 44.6 |

Between Subjects Differences in Motor Planning

| Region | Hem | BA | Volume (mm3) | F5, 54 | SEM | Talarach Coordinates (RAI) | | |
|--------------------|-------|----|-----------------|--------|--------|----------------------------|------|------|
| | | | | | | x | y | z |
| Post central Gyrus | Right | 3 | 944 | 6.0774 | 0.0768 | -53.9 | 16.7 | 38.5 |
| Post central Gyrus | Left | 2 | 600 | 5.7431 | 0.0772 | 39.9 | 36.7 | 58.8 |
| Post central Gyrus | Left | 5 | 248 | 5.3594 | 0.0433 | 30.4 | 42.5 | 70.1 |
| Precentral Gyrus | Left | 6 | 152 | 7.558 | 0.5526 | 46 | 3.1 | 54.4 |
| Precentral Gyrus | Left | 6 | 64 | 9.0165 | 0.8579 | 44.1 | 7.1 | 52 |

Motor Execution: Adults Within-Subjects

| Region | Hem | BA | Volume (mm3) | F5, 144 | SEM | Talarach Coordinates (RAI) | | |
|--------------------------|-------|----|-----------------|---------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Parietal Lobule | Right | 40 | 928 | 4.7514 | 0.0364 | -44.7 | 54.8 | 54.3 |
| Inferior Frontal Gyrus | Right | 44 | 400 | 4.5111 | 0.0303 | -50.8 | -23.2 | 36.3 |
| Post central Gyrus | Left | 2 | 288 | 5.4528 | 0.1553 | 27.3 | 36 | 72.3 |
| Precentral Gyrus | Right | 6 | 184 | 4.8537 | 0.0992 | -59.8 | 0 | 29.3 |
| Post central Gyrus | Left | 3 | 48 | 4.7529 | 0.2004 | -42.4 | 18.9 | 49.7 |

Motor Execution

| Region | Hem | BA | Volume (mm3) | F11, 318 | SEM | Talarach Coordinates (RAI) | | |
|--------------------------|-------|----|-----------------|----------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Parietal Lobule | Right | 40 | 2168 | 4.8243 | 0.0254 | -62.3 | 39 | 28 |
| Superior Frontal Gyrus | Left | 6 | 1544 | 4.5796 | 0.0178 | 28 | 9.1 | 63.6 |
| Middle Frontal Gyrus | Left | 9 | 1096 | 6.0793 | 0.1441 | 49.1 | -3.7 | 39.1 |
| Superior Parietal Lobule | Right | 2 | 1064 | 4.5741 | 0.0244 | -20.8 | 44.1 | 75.2 |
| Inferior Frontal Gyrus | Left | 45 | 704 | 4.7425 | 0.0434 | -22 | 2.8 | 69 |
| Precentral Gyrus | Right | 6 | 648 | 4.824 | 0.049 | 53.8 | -24.9 | 4.8 |
| Inferior Parietal Lobule | Left | 40 | 440 | 5.8381 | 0.1646 | -54.1 | -3.4 | 30.8 |
| Superior Frontal Gyrus | Left | 8 | 304 | 4.538 | 0.0378 | 65.5 | 23.3 | 19.9 |
| SMA | Right | 6 | 248 | 4.4821 | 0.0475 | 35.3 | -25.4 | 49.8 |
| Precentral Gyrus | Right | 6 | 128 | 4.9403 | 0.1387 | -6.6 | 6.5 | 82 |
| Middle Frontal Gyrus | Left | 6 | 72 | 4.3127 | 0.0369 | -60.7 | 12.5 | 40.7 |

Between Subjects Differences in Motor Execution

| Region | Hem | BA | Volume (mm3) | F7, 202 | SEM | Talarach Coordinates (RAI) | | |
|------------------------|-------|----|-----------------|---------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Inferior Frontal Gyrus | Right | 44 | 4328 | 6.4822 | 0.0577 | -56.9 | -11.9 | 4 |
| Precentral Gyrus | Left | 6 | 1800 | 5.1119 | 0.0497 | 39.3 | 14.8 | 58.6 |
| Middle Frontal Gyrus | Left | 6 | 1072 | 4.5313 | 0.0183 | 27.7 | -16.1 | 57.7 |
| Precentral Gyrus | Left | 4 | 424 | 4.8063 | 0.0538 | 57.8 | 11.7 | 28 |
| Post central Gyrus | Right | 1 | 320 | 5.1824 | 0.1175 | -52.6 | 16.7 | 51.1 |
| Superior Frontal Gyrus | Left | 8 | 128 | 4.7211 | 0.0901 | 36.4 | -26.7 | 49 |
| Inferior Frontal Gyrus | Right | 47 | 56 | 5.4303 | 0.2689 | -53 | -21.7 | -6.3 |

Motor Execution: Children Within-Subjects

| Region | Hem | BA | Volume (mm3) | F 16, 175 | SEM | Talarach Coordinates (RAI) | | |
|---|-------|----|-----------------|-----------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Middle Frontal Gyrus | Right | 6 | 2968 | 6.274 | 0.0985 | -41.8 | -0.5 | 47.8 |
| Inferior Parietal Lobule | Left | 40 | 2312 | 6.7067 | 0.1316 | 49.3 | 35 | 54.3 |
| Middle Frontal Gyrus | Right | 9 | 816 | 5.3299 | 0.0881 | -43 | -16.4 | 40.2 |
| Precentral Gyrus | Left | 6 | 816 | 6.8457 | 0.3053 | 44.6 | -4.6 | 46.3 |
| Post central Gyrus | Right | 2 | 576 | 4.9405 | 0.0635 | -44.6 | 36 | 58.6 |
| Supramarginal Gyrus | Left | 4 | 520 | 5.7241 | 0.1338 | 56.1 | 17.9 | 39 |
| Inferior Frontal Gyrus (pars opercularis) | Right | 44 | 400 | 5.4012 | 0.1168 | -47.3 | -12.5 | 25.6 |
| Supplementary Motor Area | Left | 6 | 232 | 4.5663 | 0.0662 | 8.6 | 8.4 | 68.3 |
| Inferior Frontal Gyrus (pars opercularis) | Left | 45 | 200 | 5.1311 | 0.1535 | 52.7 | -16.4 | 28.3 |
| Supramarginal Gyrus | Left | 40 | 184 | 4.6276 | 0.0564 | 62.4 | 23.7 | 27.3 |
| Precentral Gyrus | Left | 6 | 184 | 5.1748 | 0.1446 | 31.7 | 16.1 | 69.3 |
| Post central Gyrus | Left | 6 | 96 | 6.287 | 0.343 | 20 | 25.4 | 72.5 |
| Precentral Gyrus | Left | 4 | 88 | 4.7455 | 0.1214 | 56 | 4 | 28 |
| Supramarginal Gyrus | Left | 40 | 72 | 4.4312 | 0.048 | 61.3 | 20.7 | 17.6 |
| Superior Frontal Gyrus | Left | 6 | 72 | 4.5727 | 0.1053 | 16.7 | -9.2 | 65.2 |
| Precentral Gyrus | Right | 4 | 40 | 4.6226 | 0.1835 | -53.6 | 10 | 50.8 |

Motor Execution

| Region | Hem | BA | Volume (mm3) | F 9, 98 | SEM | Talarach Coordinates (RAI) | | |
|--|-------|----|-----------------|---------|--------|----------------------------|-------|------|
| | | | | | | x | y | z |
| Precentral Gyrus | Right | 6 | 1056 | 5.7369 | 0.1029 | -48.4 | -1.8 | 43.8 |
| Precentral Gyrus | Right | 6 | 536 | 5.643 | 0.1283 | -51 | -3 | 32 |
| Post central Gyrus | Right | 3 | 464 | 5.656 | 0.1522 | -25.5 | 27.4 | 69.5 |
| Middle Frontal Gyrus | Left | 9 | 312 | 5.4656 | 0.1877 | 50.7 | -8.5 | 34 |
| Inferior Frontal Gyrus (pars opercularis) | Left | 44 | 224 | 4.9063 | 0.1186 | 54.7 | -6.6 | 13 |
| Inferior Frontal Gyrus (pars opercularis) | Right | 44 | 96 | 4.6507 | 0.0935 | -41.3 | -15.2 | 27.1 |
| Inferior Frontal Gyrus (pars opercularis) | Right | 44 | 80 | 4.6466 | 0.1716 | -47.7 | -21.9 | 29.4 |
| Inferior Frontal Gyrus (pars triangularis) | Left | 45 | 72 | 4.4032 | 0.0703 | 54.9 | -23.3 | 24.9 |
| Precentral Gyrus | Right | 4 | 40 | 4.4355 | 0.1026 | -35.2 | 23.2 | 53.6 |

Between Subjects Differences in Motor Execution

| Region | Hem | BA | Volume (mm3) | F 16, 175 | SEM | Talaraich Coordinates (RAI) | | |
|--------------------------|-------|----|-----------------|-----------|--------|-----------------------------|-------|------|
| | | | | | | x | y | z |
| Middle Frontal Gyrus | Right | 9 | 1608 | 6.8758 | 0.1403 | -43.5 | -21.3 | 33.7 |
| Post central Gyrus | Right | 1 | 1408 | 5.1415 | 0.0591 | -35.2 | 32.7 | 62.9 |
| Paracentral Lobule | Right | 6 | 888 | 5.4089 | 0.0775 | -13.3 | 21.5 | 76 |
| Post central Gyrus | Left | 1 | 424 | 5.1223 | 0.0756 | 56.7 | 26.9 | 50.6 |
| Inferior Parietal Lobule | Right | 40 | 368 | 5.2059 | 0.1239 | -52.1 | 39.3 | 50.3 |
| Precentral Gyrus | Left | 6 | 312 | 4.694 | 0.045 | 23.1 | 15.1 | 70.8 |
| Middle Frontal Gyrus | Left | 6 | 240 | 5.2053 | 0.1648 | 45.5 | -4.9 | 45.4 |
| Precentral Gyrus | Right | 6 | 200 | 5.1046 | 0.1681 | -53.2 | -0.3 | 44.5 |
| Precentral Gyrus | Right | 6 | 200 | 6.9103 | 0.485 | -34.6 | 10.1 | 62 |
| Precentral Gyrus | Left | 4 | 152 | 6.2202 | 0.4657 | 60.4 | 3.9 | 27.5 |
| Inferior Parietal Lobule | Left | 40 | 120 | 4.8258 | 0.1099 | 63.5 | 23.4 | 24.6 |
| Precentral Gyrus | Left | 6 | 88 | 4.5457 | 0.0476 | 42.4 | 15.6 | 64.4 |
| Post central Gyrus | Left | 2 | 64 | 5.2369 | 0.3908 | 45 | 39.2 | 67.1 |
| Precentral Gyrus | Left | 4 | 56 | 4.549 | 0.0838 | 58.3 | 18 | 38.9 |
| Supplementary Motor Area | Left | 6 | 48 | 4.6165 | 0.1867 | 2 | 5.3 | 72.4 |
| Middle Frontal Gyrus | Left | 6 | 40 | 4.8332 | 0.2356 | 39.2 | 1.6 | 58.1 |

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