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Examination of Cerebral Hemodynamics of School-Aged Children Who Do and Do Not Stutter During Reading: a Near-Infrared Spectroscopy Pilot Study

by

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Abstract

This exploratory pilot study examined the reliability of using functional near-infrared spectroscopy (fNIRS) to evaluate cerebral hemodynamic responses of oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (HHb), hemoglobin difference (HbDiff) and total hemoglobin (tHb) in the left inferior frontal region during silent and out loud reading in 15 typically fluent school-aged children (TFC). Hemodynamic responses of 4 children who stutter (CWS) were also compared to matched TFC.

In TFC, fNIRS was found to reliably measure changes in all cerebral hemodynamic variables during out loud reading, but only HbO_2 and tHb during silent reading. Comparisons between CWS and matched TFC revealed no clear differences, except for group differences in the out loud condition, in which CWS exhibited consistent neuronal deactivation more frequently than matched TFC. The findings of this study provide support for the feasibility and reliability of using fNIRS to measure neural function in TFC during out loud reading.

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CHAPTER 1: LITERATURE REVIEW

Developmental Stuttering

Developmental stuttering begins in early childhood, usually between the ages of 2 and 5 (Buchel & Sommer, 2004). It is characterized by involuntary interruptions in speech in the form of repetitions of sounds (e.g., "m-m-m-mom"), syllables (mo-mo-mo-Mom), words (e.g., "my-my-my mom"), prolongation of sounds (e.g.,"yyyyyyyyyy-ellow"), or silent blocks. Stuttering is also often accompanied by a host of observable secondary features that include eye blinks, head jerks, and facial grimaces; these features are even found in very young children (Zebrowski, 1995). Schwartz and Conture (1988) studied 43 children who stuttered between the ages of 3 and 10, and found that all of them displayed concomitant non-speech behaviours, regardless of how developed their stuttering was. These findings were also replicated by Yairi and Ambrose (1993), who studied children under 6 years of age and found that all of them displayed secondary features, in the form of head and facial movements, during stuttered speech.

With an overall prevalence of 0.72% (Craig, Hancock, Tran, Craig, & Peters, 2002), and an incidence between 4 to 5% (Bloodstein & Bernstein Ratner, 2008) and 8% (Reilly et al., 2009) in preschool and school-age populations, stuttering is a fluency disorder that affects a vast number of individuals globally. Although approximately 65-80% of children who stutter (CWS) spontaneously recover within four years (Yairi &Ambrose, 1999;

Kloth, Kraaimaat, Janssen & Brutten, 1999; Prasse & Kikano, 2008), 20-30% of children who stutter develop persistent stuttering that pervades throughout their lives (Yairi & Ambrose, 1999). Factors thought to be associated with a greater likelihood of spontaneous recovery from stuttering include having: relatives who recovered from stuttering, a more stable speech motor system, stronger phonological, language and nonverbal skills, and speaking more slowly. Being female is also thought to increase the likelihood of recovery. During childhood, the male to female ratio for stuttering is 2:1. This rises to 4:1 to 5:1 in adulthood, indicating that girls are more predisposed to spontaneous recovery (Ambrose et al., 1997; Guitar, 2006; Yairi & Ambrose, 2005).

Psychological, Emotional, and Social Consequences of Stuttering

Stuttering has psychological, emotional, and social consequences. Frustration is common to individuals of all ages who stutter (Bloodstein & Bernstein Ratner, 2008; Langevin, Packman, & Onslow, 2010). In addition, many adults experience social anxiety (Blumgart, Tran & Craig, 2010; Menzies, Onslow, & Packman, 1999; Stein, Baird, & Walker, 1996) along with fear of negative evaluation (Messenger, Onslow, Packman & Menzies, 2004). They often feel that their stuttering has negatively impacted their relationships with others and has limited them from reaching their occupational potential (Klompass &Ross, 2004; Klein &Hood, 2004; Peters & Starkweather, 1989).

Like adults who stutter (AWS), CWS also experience the psychological, social and emotional impact of stuttering even at an early age. Compared to their non-stuttering peers, school-age children who stutter are more likely to be teased (Blood & Blood, 2007; Hugh-Jones & Smith, 1999; Langevin, Bortnick, Hammer, & Wiebe, 1998) and are less likely to be accepted socially or be perceived as leaders (Davis, Howell & Cook, 2002). They also are perceived negatively by their peers (Langevin, 2009; Langevin, Kleitman, Packman & Onslow, 2009). Long-term consequences of these childhood experiences include feelings of anxiety, shame, depression, loss of self-confidence and self-esteem and social avoidance and withdrawal (Hugh-Jones and Smith, 1999). Regarding preschoolers, recent observational and survey studies found that stuttering elicited negative peer responses that included walking away from the child who stutters, not waiting for them to finish talking, and teasing (Langevin, Packman, & Onslow, 2009; 2010).

Causal Underpinnings of Stuttering

Although stuttering has been the subject of much research, to date, the exact cause of stuttering is unknown. Advances in genetic and neuroimaging research are providing important indications of neurophysiological bases of stuttering; however, a simple model of genetic transmission is unlikely, and the role of environment cannot yet be ruled out (Büchel & Sommer, 2004; Suresh, et al., 2006).

Genetic and environmental influences. It is already well established that genetics play a role in the prevalence of stuttering, such that the majority of people who stutter (PWS) have relatives who stutter (Ambrose, Yairi & Cox, 1993; Viswanath, Lee & Chakraborty, 2004). When stuttering runs in families, the genetic closeness between family members predicts the occurrence of the disorder (Kidd, 1980). Twin studies also have shown that even at the young age of 3, there is a higher concordance of stuttering in identical twins (70%) than in fraternal, same-sex twins (30%) or siblings of the same sex (18%) (Andrews, Morris-Yates, Howie & Martin, 1991; Felsenfeld et al., 2000; Dwarnzynski, Remington, Rijsdijk, Howell, & Plomin, 2007). This suggests that there may be some traits that are passed down that predispose a child to develop stuttering. Such traits have been posited to be a predisposition for repetitive speech, a tendency to react negatively to repetitious speech (Starkweather, 2002), a predisposition for rapid speech (Kloth, Jansen et al., 1998), low tolerance for frustration, and slow vocal and manual reaction times (Starkweather, 2002). Although quite preliminary, advances in genetic research have been made, including the identification of a linkage to three genes in chromosome 12 (Dranya, 2011; Kang et al., 2010; Riaz et al., 2005), as well as sex-specific linkages to chromosome 7 in males and chromosome 21 in females, suggesting that the genetic component to stuttering may have significant sex effects (Suresh et al., 2006).

Despite evidence of a genetic root of stuttering, the fact that there is discordance in some identical twin pairs shows that genetics alone do not

explain stuttering. Studies have shown that while genetic effects account for approximately 70% of the probability of whether a child will develop persistent stuttering, environmental influences such as stress during pregnancy, low birth weight, childhood illness, and negative parental reaction to stuttering may have unique effects on different children when the genetic liability of stuttering is present. Environmental influences are said to account for approximately 30% of the variance of whether or not a child will develop stuttering (Dwarnzynski et al., 2007; Felsenfeld et al., 2002; Guitar, 2006). Environmental influences can either be unique to the individual, or shared between children within the same family. Shared factors make children more like each other, while unique factors make them different from one another (Dwarnzynski et al., 2007).

Neurophysiological factors. The idea that stuttering has a neurophysiological basis has been around for decades. The Orton-Travis concept stated that stuttering results from an underlying condition in which a lack of cerebral dominance causes the bilaterally paired musculatures of the speech organs to work independently of each other (Orton & Travis, 1929; Bloodstein & Bernstein Ratner, 2008). Moore (1984) proposed that each hemisphere had a specialization. The right hemisphere was specialized for time-independent, non-segmental information, while the left hemisphere was specialized for the processing of time-dependent, segmented stimuli. According to this hypothesis, disfluent speech results from using the unsuitable right hemisphere for speech-processing. This hypothesis was

supported by studies that found that both children and adults who stutter had activation patterns that were lateralized to the right hemisphere during linguistic tasks as well as dichotic listening tasks, while typically fluent speakers showed primarily left hemisphere activation (Moore, 1986; Cimorell-Strong, Gilbet, & Frick, 1983). This atypical lateralization of speech and language processes was shown to shift to more typical left hemispheric regions following fluency therapy (Boberg, 1993), indicating that this tendency was a "manipulable process, rather than a static disorder resulting from CNS [central nervous system] dysfunction" (Moore, 1984, p. 49).

More recently, structural and functional neuroimaging techniques have allowed researchers to more directly investigate the involvement of the left and right hemispheres and cortical and subcortical brain regions in stuttering. Structural neuroimaging examines the anatomical structure of the brain, and is, therefore, highly valuable as a diagnostic tool. Functional neuroimaging, on the other hand, allows for the visualization of brain activity during the planning or execution of a specific task or function (Neumann & Euler, 2009).

Models of Speech Production

A theoretical framework of the processes involved in speech production is useful for understanding the findings of neuroimaging studies within the stuttering population. Existing models of speech production focus on the linguistic aspects of speech production (i.e., syntactic, semantic and

phonological processing), or on the execution of articulatory processes (Rapp & Goldrick, 2006; Beal, 2010). In the case of the former, the psycholinguistic models proposed by Levelt (Levelt, Roelofs, & Meyer, 1999) and Dell (Dell & O'Seaghdha, 1992) are the most prominent. Although there are variations between these models, there is general consensus that, broadly speaking, speech production involves activation of lexical or conceptual representation, followed phonological encoding and, finally, articulatory encoding. Given that the present study is focused on developmental stuttering, and given the difficulties stuttering speakers have in auditory processing and the planning, execution and self-monitoring of speech-motor production (Brown, Ingham, Ingham, Laird & Fox, 2005; Lu et al., 2009), models of articulation are more relevant to the present study than psycholinguistic models.

Directions into the Velocities of Articulators (DIVA) model

In terms of articulatory models, the DIVA model (Figure 1), a computational neural model of speech acquisition and production, is the most thoroughly defined and tested model (Guenther, Ghosh & Tourville, 2005; Guenther & Vladusich, 2012). Computer simulations of the DIVA model simulate both fluent and stuttered speech, and the model is anatomically defined, making it an ideal framework for understanding the roles of the brain regions involved in speech production and the findings of functional imaging studies (Civier et al., 2010). The components of the DIVA model, are

comprised of model neurons or maps, each of which are thought to correspond to a set of simultaneously firing neurons within the cerebral cortex. The output of one model neuron corresponds to the average number of action potentials per second of the set of corresponding neurons. Unlike a number of other models, the components of the DIVA model have been associated with specific neuroanatomical locations. The localization of these maps is based on the results of neuroanatomical and neurophysiological studies of speech production and articulation.

According to the DIVA model, the production of a speech sound (i.e., a phoneme, syllable or short syllable sequence) begins with the activation of the of neurons associated with a specific sound in the *speech sound map* which is thought to lie in the posterior part of the left inferior frontal gyrus (left pIFG) and the left ventral premotor cortex (left vPMC). It is thought that brain regions involved in phonological encoding (e.g., Broca's area) are responsible for activation of the speech sound map, and that the basal ganglia is responsible for the timing of the activation (Beal, 2010; Civier et al., 2010; Guenther et al., 2005). Motor commands from the speech sound map are sent to the *articulatory velocity and position maps* in the motor cortex via two control subsystems: the *feedforward and feedback control subsystems* (Guenther & Vladusich, 2012).

The feedback control subystem relies on both auditory and somatosensory feedback. During the learning/imitation stages of speech (e.g.,

infants), auditory feedback control is solely relied on to tune the speech motor control system, as there are no existing accurate feedforward commands. An auditory target (i.e., how an utterance should sound) is learned and encoded in projections from the speech sound map to the *auditory error map*. (Civier, Tasko & Guenther, 2010; Guenther & Vladusich, 2012). According to DIVA model predictions, these projections are learned quickly and remain stable over long periods. Signals are sent from activated neurons in the speech sound map corresponding to the sound to auditory cortical areas. Continuous comparison is made between the auditory target and the incoming auditory feedback from speech output, and is sent to the *auditory state map.* Discrepancies between the two result in the activation of neurons in the auditory error map, and resulting corrective motor commands are sent from the *feedback control map* to *articulatory velocity maps* in the motor cortex. The auditory state map and error map are said to be located in the primary auditory cortex, including Heschl's gyrus (HG), posterior superior temporal gyrus and sulcus (pSTG and pSTS) and planum temporale (PT). Each attempt to produce the sound updates command signals in the feedforward control substyem, resulting in feedforward commands with less auditory errors. When speech production no longer elicits auditory errors, the auditory feedback control subsystem is not invoked, as accurate feedforward commands have been learned. However, in the event of any external perturbations (e.g., externally altered auditory feedback or change in size and shape of articulators during the lifespan), auditory error neurons

become activated and attempt to correct for the perturbation (Guenther & Vladusich, 2012).

The somatosensory feedback control system works alongside the auditory feedback control subsystem. Repeated production of an accurate speech sound results in the learning of a somatosensory target (i.e., sensory expectation of how an utterance should feel) (Civier et al., 2010; Guenther & Vladusich, 2012). As simply listening to or watching another person speak is not sufficient to know how an utterance should feel, somatosensory targets, unlike auditory targets, are learned through self-monitoring following the learning of accurate feedforward commands via auditory feedback control. A mismatch between the desired somatosensory target and the tactile and proprioceptive feedback information in the somatosensory state map results in the activation of *somatosensory error map* neurons. Corrective motor commands are then issued to the motor cortex via the feedback control map. The somatosensory state map and error map are said to be located in the supramarginal gyrus (SMG) of the inferior parietal cortex (Guenther & Vladusich, 2012).

In the feedforward control subsystem, the speech sound map transmits motor commands to the primary motor cortex either directly or via the cerebellum. These motor commands have been preprogrammed and 'tuned' through repeated attempts at speech sound production using feedback control (i.e., early word imitation when learning language), and do

not rely on error detection from sensory feedback. The feedback control subsystem is not employed unless speech is perturbed in some way. Resulting corrective commands serve to keep feedforward commands appropriately tuned.(Civier et al., 2010). A more recent extension of the DIVA model, the GODIVA model (Bohland, Bullock & Guenther, 2010), posits that an initation map, thought to lie within the supplementary motor area (SMA) modulates the release of motor commands to the articulatory maps via a GO signal. The magnitude of the GO signal, ranging from zero to one, is positively correlated with speaking rate. A zero GO signal prevents the transmission of speech sound map output to the primary motor cortex. (Guenther & Vladusich, 2012).

The DIVA Model and Dysfunction in the Stuttering Population

Researchers have hypothesized that an anomalous sensory feedback system may be responsible, in part, for stuttering . Altered auditory feedback has been found to result in dramtically improved fluency in people who stutter (Alm, 2004; Stuart et al., 2008). It is thought that unlike fluent speakers, people who stutter rely heavily on sensory feedback control. As the normal rate of speech is faster than the rate of sensory feedback, the feedback subsystem is slow to detect and correct errors (Beal, 2010; Civier et al., 2010; Guenther et al., 2006). Thus, within the framework of the DIVA model, overreliance on feedback control is thought to lead to an accumulation of errors, which then become too large to be corrected and

instead must be repaired by way of a motor "reset" that is manifested as a restarting of the syllable (i.e., repetition) (Civier et al., 2010; Guenther et al., 2006). It is proposed that the feedforward control subsystem is impaired in people who stutter, and that impaired readout of feedforward commands underlies all types of dysfluencies (Civier, 2010).

As mentioned above, speech sound neurons are said to be located within the left inferior frontal gyrus (IFG). CWS have been found to have decreased grey matter volume in this region, suggesting that they may have fewer speech sound neurons than fluent children. Interpreted within the framework of an articulatory model, this finding suggests that CWS may not be able to adequately form neural representations of speech sounds necessary for effective articulation (Beal, 2010). Findings of dereased grey matter volume in the insular cortex of CWS, an area involved in speech articulation (Guenther, 2005), and increased grey matter in this region in AWS, suggests that while CWS may have deficient resources for planning and monitoring articulation, AWS heavy reliance on the monitoring of speech production may have resulted in compensatory increases in insular grey matter volume (Beal, 2010).

Functional Neuroimaging Research with AWS

Findings of Functional Neuroimaging Studies with AWS

Although it is clear that there are neurophysiological differences between people who stutter and fluent speakers (Ingham, Cykowski, Ingham & Fox, 2008), there are still many discrepancies between the findings of functional neuroimaging studies. These discrepancies may be attributed to inter-subject variability or differences in imaging techniques, tasks or data analysis (Ingham, Grafton, Bothe & Ingham, 2012). To date, the neurological basis of developmental stuttering is still not exactly known. However, there is some agreement in the literature, converging on certain "signatures" of stuttering. These are (a) atypical right lateralization of activation of speech motor regions; (b) overactivation of right IFG and motor areas, such as the cerebellum, primary motor cortex and supplementary motor area; and (c) decreased activation in left IFG as well as auditory areas, such as the left superior temporal cortex (Braun et al., 1997; Brown et al., 2005; Fox et al., 1996; Lu et al., 2009; Neumann et al., 2005).

The basal-ganglia is also thought to play a critical role in the neural network involved in stuttering dysfunction (Lu et al., 2010). Failure of the basal ganglia to provide sufficient timing cues to the supplementary motor area is thought to be part of the core cause of stuttering (Alm, 2004).

Left IFG functional abnormalities in AWS. Research has suggested that the cause of stuttering lies not in the disturbance of any particular neural

substrate, but in dysfunctional neural interactions and connections between regions necessary for speech processing for production (Alm, 2004). One of the main regions thought to be associated with the cause of stuttering is the left IFG of the prefrontal cortex (Chang, Erickson, Ambrose, Hasegawa-Johnson & Ludlow, 2008; Ingham, Grafton, Bothe & Ingham, 2012;Kell et al. 2009; Sommer, Koch, Paulus, Weiller & Buchel, 2002). Converging structural and functional evidence suggests that a deficient left inferior frontal-premotor/motor cortex connection plays an important part in the neurophysiology of stuttering (Chang, Horowitz, Ostuni, Reynolds & Ludlow, 2011). The production of fluent speech requires proficient dynamic interactions between the cortical and subcortical systems involved in the selection, initiation and execution of necessary motor sequences (Chang et al., 2011; Watkins, Smith, Davis & Howell, 2008). These inter-regional connections have been found to be disordered and deficient in adults who stutter (Chang et al., 2011; Salmelin, et al., 1998; Lu et al. 2010; Watkins et al., 2008). It has been found that during both stuttered and perceptually fluent speech, adults who stutter have an abnormal (Golfinopoulos, Tourville, & Guenther, 2010; Salmelin, et al., 1998) and sometimes absent functional connection from the inferior frontal region to the pre-motor areas and motor areas for speech production (Chang et al., 2011). Specifically, both structural and functional connectivity analyses, using DTI and fMRI, respectively, have found white matter deficits in underlying left inferior frontal and motor areas, and deficiencies in functional connectivity between the left IFG and left

motor areas in adults who stutter compared to fluent speakers (Chang et al., 2008; 2011; Lu et al., 2009) during both speech and non-speech tasks (vocal-tract gestures). These neural anomalies associated with the cause of stuttering are thought to be task-independent and observable even during rest. Lu et al. (2012) found that AWS showed significantly lower resting state functional connectivity (RSFC) strength, relative to fluent speakers, in the pars-opercularis (PO) of the left IFG, an area associated with lexical selection, phonological processing and phonetic encoding. The IFG has been said to be involved in syllabification (Schumann, Schiller, Goebel & Sack, 2008) and phonetic encoding (Papoutsi et al., 2009), both of which are involved in planning of motor execution of speech acts (Lu et al., 2010). The right IFG, on the other hand, is mainly involved in error detection and acts as an inhibitor of speech-acts generated by the left IFG (i.e., go/no go) (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Xue, Aron, & Poldrac, 2008;). A functional and anatomical disconnection from the left IFG to the left motor areas may be related to the difficulty stuttering speakers have in forming the motor representation during speech (Lu et al., 2009). Salmelin, Schnitzler, Schmitz and Freund (2000) found that during fluent picture naming, the sequence of cortical activity between the left inferior frontal area and motor area in adults who stutter was the reverse of that observed in fluent speakers. The connection between the bilateral inferior frontal gyri and the basal ganglia, a region that modulates the activity of left motor and temporal cortices, has also been found to be altered. This suggests that the basal

ganglia is “unable to produce timing cues to the motor cortex for the initiation of the next motor segment in speech” (Lu et al., 2010, p.154) because it does not receive sufficient input from the left IFG. This, in turn, potentially exerts a negative influence on the connection between the IFG and the premotor area (Lu et al., 2010; Watkins et al. 2008).

Structural Neuroimaging Research with AWS

Findings of Structural Neuroimaging Studies with AWS

Several diffusion tensor imaging (DTI) studies have found fractional anisotropy (FA) reductions in left perisylvan white matter near the left rolandic operculum (RO) in adults who stutter (Chang et al., 2008; Cykowski, Fox, Ingham, Ingham & Robin, 2010; Sommer, Koch, Paulus, Weiller and Buchel, 2002; Watkins, Smith & Howell, 2008). Reduced white matter integrity has been found in the left ventral premotor cortex (Watkins et al., 2008). Other studies using voxel-based morphometry (VBM) have found increased increased grey matter density in the right superior temporal gyrus (Beal, Gracco, Lafaille & De Nil, 2007), and also increased white matter volume in the right superior temporal gyrus, inferior frontal gyrus, precentral gyrus and anterior middle frontal gyrus (Janke, Hanggi & Steinmetz, 2004).

Left IFG structural abnormalities in AWS. In addition to functional connections between speech-processing regions being deficient, these regions themselves have also been shown to be anatomically abnormal in

people who stutter. Using diffusion-tensor imaging, Sommer and colleagues (2002) found unusually thin left-sided white matter, specifically myelin structure, underlying the left rolandic operculum (RO). This region has been said to be necessary for effective communication between areas required for the auditory perception and execution of speech (Kell et al., 2009). According to Buchel and Watkins (2010) the reductions in white matter in this area seem to indicate a genetically rooted pathology (Chang et al., 2011). Consistent with the findings of Sommer et al. (2002) are those of Chang et al. (2008), who found that similar to adults who stutter, CWS also showed a reduction in white matter integrity in the left RO, overlapping the oral-facial motor regions in the left hemisphere. These children were also found to have reduced grey matter volume in the left IFG.

Anatomically, the left inferior frontal region of adults with persistent developmental stuttering differs from that of fluent speakers. Reduced RSFC strength in the left PO was found to be associated with reduced cortical thickness in this area, with both anomalies persisting despite behavioural intervention (Lu et al., 2012). Foundas, Bollich, Corey, Hurley and Heilman (2001) found that adults with persistent development stuttering had extra gyri, a feature that is rarely present in fluent speakers. Gyral varients included extra gyri along the superior bank of the sylvian fissure and an extra diagonal sulcus in the frontal operculum within the inferior frontal gyrus. The formation and development of gyri is a complex process that occurs during the prenatal stages, and malformations in it can be seen as indicative

of a developmental disorder (Joseph, 1996; Neumann & Euler, 2009). Cykowski et al. (2008) found more sulcal connectivity in the right Sylvian fissure of adults with persistent developmental stuttering. Sulcal connectivity in the right Sylvian fissure has been shown to be positively correlated with stuttering severity suggesting that the severity of stuttering may be related to abnormal development processes in the right perisylvian region (Cykowski et al., 2008).

The inferior frontal region of adults who stutter also differs bilaterally in that increased white matter volume has been found in the right hemisphere (Janke, Hanggi & Steinmetz, 2004), while reduced grey matter has been found in the left hemisphere (Kell et al., 2009). Kell et al. (2009) found that reductions of grey matter in the left IFG were positively correlated with stuttering severity, suggesting that the left inferior frontal region is associated with the origin of stuttering. CWS have also been found to have reduced grey matter volume in the left frontal cortex (Chang et al., 2008). While an addition of functioning brain tissue has been said to represent some sort of adaptation, reductions in brain tissue are thought to be indicative of a primary lesion (May & Gaser, 2006). Unlike adults who stutter, however, CWS show no increases in brain tissue in right hemisphere regions, suggesting that left hemisphere anomalies are the ones related to the cause of stuttering (Chang et al., 2008; Kell et al. 2009). According to Chang et al. (2008), given the possibility for neural structures to transform as a result of alterations in behaviour and brain function, enlargements of right

hemisphere regions in adults who stutter might be an adaptation resulting from long-term persistent stuttering, and a possible result of extensive practice of a behaviour (Draganski, et al., 2004). Structural brain differences are thought to accompany differences in functional activation (Beal, Graco, Lafaille, & De Nil, 2007), and functional evidence also suggests that the right hemisphere anomalies of over-activation during speech and increased white matter that are commonly seen in AWS (Braun et al. 1997; Brown, Ingham, Ingham, Laird & Fox, 2005; De Nil, Kroll, Kapur & Houle, 2000; Fox et al., 1996), but not in school-aged CWS (Chang et al., 2008), are not in themselves related to the cause of stuttering, but rather, are the result of a spontaneous compensation attempt for left-hemisphere deficiencies (Braun et al. 1997). The deficits seen in both children and adults who stutter, specifically in the development of white matter below the hemispheric sensorimotor areas representative of the oral-facial motor regions (Chang et al., 2008; Sommer et al., 2002) along with the reduction of grey matter in the left inferior frontal region (Chang et al., 2008; Kell et al., 2009) may indicate a lesion associated with stuttering, particularly in the integration of articulatory planning and sensory feedback, and the execution of articulatory movements (Neumann & Euler, 2009).

When studying the various stages of speech production, Chang, Kenney, Loucks and Ludlow (2009) found that people who stutter showed decreased neural activation in frontal and temporoparietal regions during perception and planning stages. These regions are those needed for the

preparation of motor responses, suggesting that people who stutter have "brain function differences during the pre-articulatory phase of production" (p. 209), and that these differences in brain activation are not specific to speech. When examining planning and execution separately, Lu, et al. (2010) found the left IFG, specifically, to be involved in the atypical planning process in stuttering.

In summary, both structural and functional imaging studies have provided evidence that implicates the left inferior frontal region as being related to the pathology of stuttering. It seems that the "neuropathophysiology of stuttering may involve deficient connectivity among the cortical network of regions that normally allows left-sided engagement of the inferior frontal and premotor cortices for efficient planning and execution of sound production" (Chang et al., 2011, p. 10) and that previously reported right hemisphere differences are likely the result of compensatory functional responses to deficient connections in the left frontal region. Chang et al. (2011) further suggest the value of conducting research with young children closer in age to symptom onset.

Functional and Structural Neuroimaging Research with CWS

Despite the wealth of information on the neurophysiology of stuttering in adults, there is very little that is known about the neurophysiology of CWS. To date, there are only six published studies (Beal, 2010; Chang et al., 2008; Kaganovich, Hampton Wray & Weber-Fox, 2010;

Mock et al., 2012; Sato et al., 2011; Weber-Fox, Spruill, Spencer, & Smith, 2008) that investigate the neurophysiological differences between school-age CWS and their fluent counterparts. Of these studies, only one has placed focus on the left IFG, despite its often-conjectured role as one of the underlying causes of stuttering.

Findings of Neuroimaging Studies with CWS

Functional imaging with CWS has shown that there is a positive correlation between the neural resources needed to process vowel stimuli and stuttering severity, suggesting that stuttering may be the result of the speech-production system relying on inefficient or less accurate resources for the planning and execution of speech (Beal, 2010). An ERP study by Kaganovich et al. (2010) found that CWS differ from their peers in the processing of non-linguistic auditory information, such that they may be more inefficient in their detection of auditory change. In an fNIRS study, both preschool and school-aged CWS showed abnormal functional lateralization for auditory processing, with hemodynamic responses being larger in the right hemisphere during a phonemic condition, and larger in the left hemisphere during a prosodic condition; the reverse was seen in fluent controls (Sato et al., 2011). Another ERP study found that CWS also exhibit atypical neural processing related to phonological rehearsal and target word anticipation (Weber-Fox et al., 2008). With regards to brain symmetry, Mock et al. (2012) found that most male school-aged CWS showed atypical brain

asymmetry, (i.e., L>R prefrontal and R>L parietal-occipital lobe), as well as greater right hemisphere white matter volume than fluent controls. However, these findings conflict with those of Chang et al. (2008), who found no differences in brain asymmetry between school-aged male CWS and fluent controls.

Left IFG abnormalities in CWS. In addition to the observation of reduced grey matter in the left IFG as mentioned earlier, Chang et al. (2008) found CWS to have increased grey matter in the right insula and decreased grey matter both in the left superior temporal gyrus as well as bilaterally in the planum temporale. These findings with CWS are, to some extent, in contrast with the structural findings with adults who stutter, in whom the left superior temporal gyrus and right planum temporal have been found to have increased grey matter (Beal et al., 2007).

Collectively, the findings of these studies suggest that there are structural and functional differences in the regions of the brain related to speech production and language processing between school-age CWS and their fluent counterparts. Also, it seems that there are similarities and differences between what is known about the neurophysiology of adults who stutter and CWS. The concurrence and discrepancies between the findings for adults who stutter and CWS both strongly underscore the need for further research with CWS, so as to determine which are causal and which are consequential features of stuttering. In particular further research is needed

with children who are closer in age to the onset of stuttering. Such research will yield vital information about the role that atypical neural processing plays in stuttering. This knowledge of the neurophysiology of stuttering in children may also allow for more effective treatment, and will provide an explanation of individual differences in terms of responsiveness to treatment (De Nil, 1999).

Neuroimaging Techniques

One of the major reasons for the lack of existing brain imaging research with CWS is the invasiveness of existing brain imaging techniques. Both positron-emission topography (PET) and single-positron emission computed tomography (SPECT) require the injection of radioactive isotopes into the bloodstream. Despite its good spatial resolution, functional magnetic resonance imaging (fMRI) has strict limitations due to movement artifacts during speech and high levels of scanning noise than can interfere with speech production. Since these technologies are often invasive, highly confining, noisy or not portable, which requires them to be used in a high-tech medical setting, they are extremely difficult to use with young children (Lloyd-Fox, Blasi & Elwell, 2010).

Functional Near-Infrared Spectroscopy

In recent years, a non-invasive optical technique has become available. Functional near-infrared spectroscopy (fNIRS) uses near-infrared light to measure oxygenation of brain tissue and hemodynamic changes associated with neural activity (Villringer & Chance, 1993). The near-infrared light penetrates the superficial layers of the body and is either scattered within the tissue or absorbed by chromophores (light absorbers). In the near-infrared region, two important chromophores, in terms of oxygenation, are oxygenated hemoglobin, which primarily occurs at a wavelength of 850 nm, and deoxygenated hemoglobin, which primarily occurs at a wavelength of 760 nm (Bhambhani et al., 2006; Gersten et al., 2011). The difference in light absorption spectra between oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb) within the near infrared spectrum allows for measurement of the changes in the concentration of the substances in living tissues. Assuming that the scattering of light in tissue is constant, as tissue geometry is unlikely to change during a brief fNIRS measurement, the measured changes in attenuation (i.e., the decrease in the intensity of emerging light) reflect the amount of absorption in targeted cerebral areas (Lloyd-Fox et al., 2010; Owen-Reece et al., 1999). While the difference in tissue absorbency between the two wavelengths (HbDiff) provides an index of oxygen utilization at the level of the small blood vessels (i.e., cerebral oxygenation), the sum of the absorbencies at the two wavelengths (tHb) is an indirect measure of localized blood volume. Since fNIRS provides levels of

oxygenated and deoxygenated hemoglobin separately, it provides additional information about the hemodynamic response (Perrey, 2008). Increased neuronal activation is associated with an increase in HbO_2 and a concomitant decrease in HHb, and is accompanied by enhanced cerebral glucose and oxygen utilization during the task (Dalsgaard & Secher, 2007).

As a result of being portable, cost-effective, non-invasive and allowing for the collection of real-time data, fNIRS is an important tool for the functional mapping of brain activity. fNIRS has high temporal resolution and reasonable spatial resolution, although the spatial resolution of fMRI is higher.

Validity of fNIRS. Previous studies have found fNIRS data to be consistent with fMRI data (Strangman, Culver, Thompson & Boas, 2002; Leff et al., 2011). Several studies have used fNIRS to evaluate cerebral hemodynamic changes during verbal fluency tasks such as rapid automatized naming and word generation from letters or semantic categories (Kohmura et al., 2013; Marumo et al., 2013). fNIRS has also been used successfully with epileptic children and adults (Gallagher et al., 2007), deaf children (Sevy, Bortfeld, Huppert, Beauchamp, Tonini and Oghalai, 2010), children with congenital heart disease (Chakravarti, Srivastava and Mittnacht, 2008), the elderly (Sakatani, Lichty, Xie, Li, & Zuo, 1999) and with a number of other clinical populations including those diagnosed with depression (Hermann, Ehlis & Fallgatter, 2004), schizophrenia (Kubota et al., 2006), pervasive

developmental disorder (Kuwabara et al., 2006), bipolar disorder (Matsuo et al., 2007), and post-stroke aphasic patients (Sakatani, Xie, Lichty, Li & Zuo, 1998). fNIRS has also successfully been used in several studies with neonates (see Lloyd-Fox et al., 2010 for a review), including an investigation of neonatal speech processing (Pena et al., 2003), These studies support the use of fNIRS as a valid, reliable and clinically useful optical imaging technique to investigate neurological differences in a population of interest. Although there is a preliminary study on the use of fNIRS with adults and children with developmental stuttering (Sato et al., 2011), no further studies have been conducted to explore its usefulness with CWS.

Concurrent fNIRS and fMRI studies. Several studies have concurrently measured cerebral hemodynamics with fNIRS and fMRI, and have assessed the correlation between changes in hemodynamic responses measured by fNIRS, especially HbO^2 and HHb, with changes in the BOLD signal. Spatial and temporal correlations (i.e., regions of activation and time-course of signals) between cerebral hemodynamic changes measured with fNIRS and the BOLD response measured by fMRI have been examined (Cui, Bray, Bryant, Glover & Reiss, 2011; Heinzel et al., 2013; Kleinschmidt et al., 1996; Strangman et al., 2002; Toronov et al., 2003). A decrease in HHb has been found to be most strongly correlated with an increase in the BOLD signal in some studies, with the time course of both signals also being correlated (Kleinschmidt et al., 1996; Toronov et al., 2003). Other studies have reported HbO_2 as being more spatiotemporally correlated with the

BOLD signal (Hoshi et al., 2011; Strangman et al., 2002). As well, examination of the overlap between regions of activation as indicated by fNIRS and fMRI has yieled findings of high consistency between the two measurement modalities (Heinzel et al., 2013; Leff et al., 2010).

Reliability of fNIRS. Although the reliability of fNIRS has not been widely agreed upon, it has been shown to provide reliable measures of cerebral oxygenation in various areas of the brain (Calderon-Arnulphi, Alaraj & Slavin, 2009). For example, fNIRS has shown fair to excellent test-retest reliability (intraclass correlation coefficients of .42 to .87) in measuring changes in cerebral oxygention in the bilateral frontal area during hyperventilation and various cognitive and verbal tasks such as word repetition, word generation and drawing of novel figures (Watanabe, Matsuo, Kato & Kato, 2003), and in the cortical areas associated with verbal fluency (Ruocco et al., 2010). High reproducibility has been shown in measuring hemodynamic changes in sensorimotor cortex of healthy adults (Sato et al., 2007). However, Schecklmann et al. (2008), in assessing the reliability of fNIRS measures of resting state functional connectivity (RSFC), found that map-wise and cluster-wise reliabilities were greater than those from single-channel measurements. A few studies have also examined the reliability of fNIRS measures over a variety of time spans during verbal fluency tasks and in response to motor stimulation (Durduran et al., 2004; Kamayama et al., 2006; Plichta, Heinzel, Ehlis, Pauli, & Fallgatter, 2007; Strangman et al., 2002). Several factors can affect the reliability of fNIRS measures. These

include variability in probe placement within subjects from one session to the other (Leff et al., 2011) and interference from extra-cranial tissue (Kahraman et al., 2006).

Overall, although fNIRS has proven to be a reliable measure of cerebral hemodynamics in some cases (e.g. Sato et al., 2007) it has also been shown to be less desirable in others (e.g. Schecklmann et al., 2008). It is evident that further research is needed to establish the test-retest reliability of fNIRS, especially at the single-channel level.

Summary

To date, relatively little is known about brain structure and function of school-age CWS. There is a strong need for further studies in this area so that there can be a better understanding of how various factors contribute to the development of the disorder, spontaneous recovery and remission through therapy. fNIRS is a promising technique for conducting non-invasive functional research with children.

Purpose and Hypotheses

The purpose of this exploratory study was to: (1) investigate the test-retest reliability of fNIRS measures of cerebral hemodynamic responses of TFC to silent and out loud reading condition, (2) examine cerebral hemodynamic

responses of TFC during reading conditions, and (3) compare cerebral hemodynamic responses of CWS and TFC during reading conditions.

The following research questions were asked:

1. TFC

a) What is the test-retest reliability of measured changes in cerebral oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (HHb), haemoglobin difference (HbDiff) and total hemoglobin (tHb), collectively referred to as cerebral hemodynamics, as measured by fNIRS during silent and out loud reading conditions? It was hypothesized that moderate to high test-retest reliabilities would be found for each of these variables during both reading conditions.

b) Is there a difference in cerebral hemodynamic responses between silent and out loud reading tasks in TFC? It was hypothesized that there would be significant differences in cerebral hemodynamic responses of TFC between silent and out loud reading conditions, with greater neuronal activation occurring during out loud reading.

2. CWS

How do cerebral hemodynamic trends within trials of reading conditions and patterns of trends across trials of reading conditions

for CWS compare to their matched controls in pair-by-pair and group comparisons? It was hypothesized that, similar to matched controls, CWS would show consistent neuronal activation during silent reading but, in contrast to matched controls, consistent neuronal deactivation during out loud reading.

CHAPTER 2: METHODS

Introduction

Although previous fNIRS studies have variably reported only one or more cerebral hemodynamic variables (e.g., only HbO_2 or various combinations of HbO_2, HHb, HbDiff, and tHb) (Kakimoto et al., 2009; Kono et al., 2007; Zhang et al. 2011), given the exploratory nature of this study, all cerebral hemodynamic variables (i.e., HbO_2, HHb, HbDiff and tHb) were analyzed.

Study Design

Participants. Participants were 15 TFC (12 females, 3 males) and 4 CWS (3 males, 1 female), with an age range of 9-12 years (TFC mean age: 11;0; CWS mean age: 10; 7). Data from a fifth CWS was removed during analysis as it was found to be invalid due to excessive head and body movement during testing. Participants were recruited through Good Shepherd Catholic School, ISTAR offices in Edmonton and Calgary, and via locally distributed information sheets and recruitment posters (Appendix A). The inclusion criteria were as follows: (a) between 9-12 years of age (b)

right-handed (c) native English speaker iv) no speech, language, reading, hearing or neurological disorders and, in the case of CWS, v) diagnosed as having persistent developmental stuttering by a qualified speech-language pathologist (SLP). Participants self-selected for this study based on having been apprised of or having read the inclusion criteria which was clearly described in the recruitment poster. Study approval was obtained from the University of Alberta Human Research Ethics Board, and approval to recruit from Edmonton Catholic Schools was obtained from the University of Alberta Cooperative Activities Program, and the Edmonton Catholic School Board.

All participants were native English speakers and were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). In order to ensure that participants had no speech or language difficulties, the Oral Speech Mechanism Screening Examination (3rd Ed.) and CELF-4 Clinical Evaluation of Language Fundamentals Screening (Semel, Wiig, and Secord, 2003) were administered by a qualified SLP. [1],[2] Sub-sections (word identification, word attack, passage comprehension) of the Woodcock Reading Mastery Test III (Woodcock, 2011) were administered by a qualified reading specialist in order to verify that participants' reading level was age and grade appropriate. Participants also had no parent-reported speech,

[1] One male CWS did not undergo Oral Speech Mechanism Screening
[2] One female (TFC 9) scored slightly below criterion on the CELF-4 Screening, but the administering SLP did not consider this child to have any language delays.

language, reading, hearing or neurological disorders, including psychogenic or neurogenic stuttering, because of the added complications associated with these disorders. Fluency in TFC was verified through parent-report and through observation by the SLP during the speech and language screening. Eight TFC who were recruited were not included in the study due to their not passing the speech-language and reading screening tests (6 children), being left-handed (1 child), and having a speech impediment (1 child).

Three of the four CWS were recruited shortly after their pre-treatment assessment and fNIRS testing was conducted prior to their commencement of treatment. The remaining child had received stuttering treatment in the past, but no treatment had been received within one year prior to participation in this study. All CWS were diagnosed with developmental stuttering by a qualified SLP during their pre-treatment assessment, and had a mean %SS of 2.39 (median: 2.03 %SS, range: 1.0-4.5% SS).

Stuttering severity for each CWS was as follows:

CWS 1: 2.02% SS

CWS 2: 1.0% SS

CWS 3: 4.5% SS

CWS 4: 2.03% SS

Procedures. Due to the lack of published fNIRS data with stuttering children, this was an exploratory experimental study. Testing protocol was developed through pilot testing with four TFC, whose data are not included in this manuscript. Testing was comprised of two sessions. The first session was the screening session in which the Edinburgh Handedness Inventory, Oral Speech Mechanism, CELF-4 Screening and Woodcock Reading Mastery Test III (Woodcock, 2011) subsections were administered. This initial session was approximately 30 minutes in length. The second session, which took place either immediately after the first session (for 10 participants) or on another day (for 5 participants), was the fNIRS measurement session. In this session, two short passages were read; one passage was read out loud (grade level 3-4) and the other read silently (grade level 1-2) (Appendix A). Both passages were of equal length at 172 syllables each. The passage assigned to each reading condition was constant, and reading order was randomized. Randomization was achieved by asking the participant to randomly select a number between 1 and 100. Even numbers corresponded to the out loud reading passage, and odd numbers corresponded to the silent reading passage. Seven of 15 TFC read the silent passage first; 3 of 4 CWS read the silent passage first. fNIRS testing commenced with a 3-minute baseline rest period. Each passage was then read twice, with a 3-minute baseline period between each reading, so as to return hemodynamic variable concentrations to baseline levels (i.e., washout period). The testing session ended with a 3-minute rest period. For the resting periods, participants were instructed to

relax with their eyes closed and remain as still as possible. Prior to testing, participants were familiarized with the fNIRS equipment and the experimental procedures. They then completed a brief practice session in which they read two short sample passages, comprised of a few sentences each (grade level 2-4; Appendix A), silently and out loud, with a rest period of 15 seconds in between readings. The fNIRS testing session was also video recorded to provide synchronized visual data for later examination of any participant factors (e.g. excessive movement) during the session. None of the participants exhibited or reported any difficulty with the testing protocol or the reading passages

Cerebral fNIRS measurements. Cerebral fNIRS measurements were recorded from the left prefrontal cortex using a single-channel fNIRS system (OXYMON, Artinis Medical Instruments, Netherlands). Optodes were placed on the left prefrontal lobe in the Fp1 position according to the 10-20 system for recording electroencephalography measurements (Herrmann , Ehlis & Fallgatter, 2004; Kuwabara et al., 2006). This probe positioning has been reported to demonstrate reliable changes in cerebral hemodynamics during verbal fluency tests in healthy individuals (Schecklmann et al., 2008). As is found in fNIRS literature, an inter-optode distance of 3 cm and a differential pathlength factor (DPF) of 5.9 were used (Sato et al., 2011; Haginoya et al., 2002; Kikuchi et al., 2013). Data were collected continuously during the reading tasks and baseline rest periods at a frequency of 10Hz and stored securely on a computer for later analysis. A moving average filter of 5

seconds was applied to the data for smoothing and reduction of any short-term movement artifacts (Kakimoto et al., 2009; Ota et al., 2012).

Participant information. The results of the present study are based on a sample of typically fluent and children who stutter, aged 9-12, This age range has been previously used in studies comparing structural and functional brain differences in stuttering and non-stuttering children (Chang et al., 2008; Weber-Fox et al., 2008). Although other stuttering studies conducted with school-aged children have used a wider age range of 6-12 years (Beal, 2010; Beal et al., 2011; Cykowski et al., 2010) this study restricted the age range to ensure sample homogeneity in terms of reading level and also to reduce the likelihood that participants at either end of the age range would find the passages too easy or too difficult.

Analyses of Cerebral Hemodynamic Responses in TFC

Qualitative Analyses of Cerebral Hemodynamic Responses

Hemodynamic trends for each trial within conditions (i.e., Silent 1, Silent 2, Out Loud 1 and Out Loud 2) were visually examined and determined as being indicative of neuronal activation, neuronal deactivation or an atypical trend. Patterns of these trends across trials within conditions (i.e., silent condition and out loud condition) were then identified as showing consistent neuronal activation, consistent neuronal deactivation or a varying

pattern (i.e., one trend in the first trial and a different trend in the second trial).

Statistical Analyses of Cerebral Hemodynamic Responses

Delta and sigma values were calculated for each reading condition and trial: Silent 1, Silent 2, Out Loud 1, and Out Loud 2. Delta values were obtained by taking the average of the trial's peak value +/- 2.5 seconds (i.e., peak average) and subtracting from it the average of the last 5 seconds of the baseline period immediately prior to onset of the respective reading task. Delta values provided a measure of the relative change in variable concentration between the resting state and the peak activity during the reading task. Sigma values were obtained by calculating the difference between each data point and the average of the last 5 seconds of the baseline period prior to the task, and then calculating the sum of these differences (i.e., the sum of the relative change from baseline of each data point.) Sigma values provided a measure of overall activity during the task.

Reliability. Bland-Altman plots were created for each condition and variable by plotting the differences between the two trials for each subject against the average of the two trials for each participant. Limits of agreement (95%) were calculated by taking the mean difference +/- 1.96 times the standard deviation (*SD*) of the mean difference. Data points that fell outside the 95% limits of agreement were considered outliers, and subsequent intra-class correlation coefficients were calculated with and without these outliers.

Test-retest reliability between trials was assessed by calculating the intra-class correlation coefficient (ICC) for the delta values and sigma values of each trial. As the intention of assessing test-retest reliability of prefrontal hemodynamic measures was to determine the replicability of a single measurement, only single measure ICCs were considered. ICC analyses were carried out using a two-way mixed model of consistency. This assesses the consistency between two measurements that are taken from random participants with a fixed measurement factor.

Differences between reading conditions and trials in TFC. A two-way repeated-measures ANOVA (condition X trial) was carried out for both the delta values and sigma values in order to determine whether there was a main effect of condition, trial or an interaction between both on the hemodynamic variables tested. Post-hoc testing using pairwise t-tests was conducted in the case of significant interactions. Statistical significance was established at an alpha level of 0.05. Effect size of significant findings was determined using partial eta-squared (η^2) according to the effect size guidelines set out by Cohen (1988). All statistical analyses were conducted using SPSS Statistics 20.0.0.

Qualitative Analyses of Cerebral Hemodynamic Responses in CWS and Matched TFC

Four CWS (3 male, 1 female; mean age: 10;7) were age and gender matched with four TFC (mean age: 11;1) Age matching was done using the participant's rounded age in years (i.e., if above 6 months, age was rounded up). Although 5 CWS were tested, the data from one male CWS was not included in the analyses due to excessive movement during the fNIRS measurement. As the sample size was not sufficient to enable quantitative analyses, only qualitative analyses of cerebral hemodynamic responses were conducted.

For CWS and matched TFC, hemodynamic trends for each trial within conditions (i.e., Silent 1, Silent 2, Out Loud 1 and Out Loud 2) were visually examined and determined as being indicative of neuronal activation, neuronal deactivation or an atypical trend. Patterns of these trends across trials within conditions (i.e., silent condition and out loud condition) were then identified as showing consistent neuronal activation, consistent neuronal deactivation or a varying pattern (i.e., one trend in the first trial and a different trend in the second trial).

Pair-by-pair comparisons of hemodynamic trends for each trial within conditions and pair-by-pair comparisons of patterns of hemodynamic trends across trials within conditions were conducted. Group differences in patterns

of hemodynamic trends were also examined.

Ethical Considerations

Consent

Prior to participating in the proposed research project, participants completed an initial familiarization session in which (a) informed consent was obtained from the participant's parent(s) and assent was obtained from the participant, (b) personal demographics were collected and (c) experimental procedures were briefly explained and outlined. A copy of the information sheet, consent form and assent form (Appendix A) were made available to the participant should they choose to keep them for their own records.

Confidentiality

All participant data were identified by a code. Only the researcher and her supervisor were aware of the identity of the participants and their code. All printed copies of data and participant forms were stored in a locked cabinet, separate from other project materials. Electronic files were stored on a password protected data storage unit. The video recordings were accessible only to the researcher, her supervisor and a research assistant. Video-recordings were stored in a locked cabinet in Dr. Langevin's laboratory at the Institute for Stuttering Treatment and Research in Edmonton. All

online participant data will be deleted and paper data will be shredded 5 years after the completion of the study.

CHAPTER 3: RESULTS

Results for the group of TFC are first presented, followed by results of the analyses of data for the CWS with their matched controls.

Qualitative and Statistical Analyses of Hemodynamic Variables in Typically Fluent Children

Qualitative Analyses of Hemodynamic Variable Trends in TFC

Hemodynamic trends of neuronal activation and deactivation were identified using conventional definitions found in fNIRS literature (Strangman et al., 2002). Neuronal activation is characterized by an increase in HbO_2 and an accompanying decrease in HHb (Figure 2a), while deactivation is characterized by a decrease in HbO_2 and an accompanying increase in HHb (Figure 2b). In this study, hemodynamic trends that were not clearly indicative of neuronal activation or deactivation were classified as being atypical. These atypical trends were characterized by similar increases and decreases in HbO_2 and HHb, (Figure 2c). Hemodynamic trends for each trial in each condition are shown in Table 1. In analyzing patterns of trends

across trials, patterns were classified as being consistent (i.e., the hemodynamic trend was the same in both trials) or varying (i.e., trends differed in the trials).

Patterns of hemodynamic variable trends between trials within the silent reading condition. The most prevalent pattern within the silent reading condition for the TFC was a varying pattern, in which hemodynamic trends differed from Silent 1 to Silent 2. For example, as shown in Table 1 and Figure 3a, the trend for TFC4 in Silent 1 shows neuronal deactivation (first A-B section in Figure 3a) whereas the trend for Silent 2 (second A-B section in Figure 3a) shows an atypical trend. Fifty-three percent (8 of 15) of the TFC demonstrated hemodynamic trends that differed from the first to second trial. The second most common pattern was that of consistent neuronal activation between trials (for example, TFC 7 in Table 1 and A-B sections in Figure 3b) with 27% (4 of 15) of TFC demonstrating this pattern. The least common pattern was that of a consistent atypical trend between trials (for example, TFC 3 in Table 1 and A-B sections of Figure 3c) with 20% (3 of 15) TFC demonstrating this pattern.

Patterns of hemodynamic variable trends between trials within the out loud reading condition. The most prevalent pattern of hemodynamic trends for TFC within the out loud reading condition was that of consistent neuronal deactivation between the two trials (for example, TFC 1 in Table 1 and C-D sections of Figure 3d), with 47% (7 of 15) of TFC

demonstrating this pattern. The second most common patterns were (a) a varying trend between trials (TFC 4 in Table 1 and Figure 3a in which the first C-D section shows neuronal deactivation and the second C-D section shows an atypical trend) with 20% of TFC (3 of 15) demonstrating this trend, and (b) a consistent atypical trend (for example, TFC 12 in Table 1 and C-D sections of Figure 3e), with 20% (3 of 15) of TFC demonstrating this pattern. The least common pattern was consistent neuronal activation (for example, TFC 5 in Table 1 and C-D sections of Figure 3f), with 13% (2 of 15) of TFC demonstrating this trend.

Statistical Analysis of Cerebral Hemodynamic Responses in TFC

Descriptive statistics for delta and sigma values for all hemodynamic variables for TFC for both reading conditions are reported in Table 2.

Reliability. As indicated above, Bland-Altman plots were created to assess agreement between trials for delta and sigma values and identify possible outliers. Due to the existence of outliers, Bland-Altman plot results are presented first, followed by ICCs with and without outliers.

Bland-Altman plots and ICCs for delta values. Bland-Altman plots for each variable comparing delta values of the two trials for each reading condition are depicted in Figure 4 (a-h). Any data points in the plots that fell beyond the 95% limits of agreement were considered outliers. In the silent condition, HbO_2 (Figure 4a) and tHb (Figure 4d) had no outliers. However, HHb had two outliers (Figure 4b) and HbDiff had one outlier (Figure 4c). In

the out loud condition, all variables had one outlier each (Figures 4e, 4f, 4g and 4h for Hbo2, HHb, Hbdiff and tHb, respectively. Examination of these outliers revealed that there was no consistency of these outliers across hemodynamic variables or reading conditions. However, TFC 2 was as an outlier in three plots (HHb silent, HHb out loud and HbDiff silent), and TFC 15 was an outlier in two plots (HbO_2 out loud and HbDiff out loud). TFC 6 and 13 were outliers once each in tHb out loud and HHb silent plots, respectively.

Intra-class correlation coefficients for delta values with and without outliers for each reading condition are presented in Table 3. For the silent condition, ICCs with outliers were .45 and .53 for HbO_2 and tHb, respectively. In contrast, ICCs for HHb and HbDiff were .01 and out of range, respectively. When existing outliers were removed from HHb and Hbdiff, test-retest reliability improved for Hbdiff with the ICC moving from out of range to .53; however, the ICC for HHb dropped out of range. ICCs for the out loud condition with outliers ranged from .53 to .84. When existing outliers in the out loud condition were removed, ICCs improved, ranging from .64 to .93.

Bland-Altman plots and ICCs for sigma values. Bland-Altman plots for each variable comparing sigma values of the two trials for each reading condition are depicted in Figure 5 (a-h). Again, any data points in the plots that fell beyond the 95% limits of agreement were considered outliers. In the silent condition, HbO_2 had no outliers (Figure 5a). However, HHb, HbDiff and tHb had one outlier each (Figure 5b, 5c, and 5d,respectively). In the out loud

condition, HbO_2 and HbDiff had no outliers (Figure 5e and 5g, respectively). However, HHb and tHb had one outlier each (Figure 5f and 5h, respectively). Examination of outliers revealed that one participant, TFC 2, was again an outlier in three plots; these were for the same reading condition and variable in which TFC 2 was identified as an outlier for delta values (HHb silent, HHb out loud and HbDiff silent). TFC 4 and 5 were outliers once each in tHb silent and tHb out loud plots, respectively.

Intra-class correlation coefficients for sigma values with and without outliers for each reading condition are presented for all hemodynamic variables in Table 3. For the silent condition, ICCs with outliers were .64 and .92 for HbO_2 and tHb, respectively. In contrast, ICCs for HHb and HbDiff were out of range. When existing outliers were removed from HHb and Hbdiff, test-retest reliability increased to .26 and .67, respectively. ICCs for the out loud condition with outliers ranged from .45 to .88. When outliers in the out loud condition were removed, ICCs improved, ranging from .45 to .91.

Differences between reading conditions and trials in TFC

ANOVA for delta values. A summary of ANOVA results for delta values is presented in Table 4. No significant differences were found for condition or trial for any of the hemodynamic variables, and there was no significant interaction between condition and trial for HbO_2, HHb, or tHb. However, a significant interaction between condition and trial was found for

HbDiff. Partial eta ^{2} for this interaction showed a large effect size of 0.35, indicating that the interaction accounted for 35% of the variance of delta values. Post-hoc testing revealed no significant differences between Trial 1 and Trial 2 in the silent condition, $t(14)= -1.11$, $p= .29$. In the out loud condition, however, the mean delta value for Trial 1 (M=1.73) was found to be significantly higher, t (14)= 2.70, p = .02, than that of Trial 2 (M=0.69) (Table 2).

ANOVA for sigma values. A summary of ANOVA results for sigma values is presented in Table 5. There were no significant interactions between condition and trial for any of the hemodynamic variables. No significant differences were found for condition or trial for HbO_2, HbDiff or tHb. However, a significant main effect of condition was found for HHb, with the mean sigma value in the out loud condition (M=270.58) being significantly higher than the mean sigma value in the Silent condition (M= -9.73). The partial eta square for this main effect showed a large effect size of 0.15, indicating that the main effect of condition account for 15% of the variance of sigma values.

Qualitative Analyses of Hemodynamic Variables in CWS and Matched Controls

CWS 1, 2, 3 and 4 were aged and gender matched with TFC 2, 4, 1, and 12, respectively. Because the sample size was insufficient to enable statistical

analyses, only qualitative analyses of hemodynamic variable trends were conducted.

Hemodynamic variable trends of CWS were categorized as being indicative of neuronal activation, deactivation, and atypical activation as described above. Pair-by-pair comparisons of hemodynamic trends for CWS and their matched controls are presented in Table 6. fNIRS graphs for each pair are found in Figure 6 (a-d).

Hemodynamic Trends by Trials and Within Conditions: Pair-by-pair Comparisons

Silent trials. As shown in Table 6, in pair-by-pair comparisons of trends within Silent 1, three of four pairs exhibited the same hemodynamic trends. Pair 2 showed neuronal deactivation (first A-B section of Figure 6b) and Pairs 3 and 4 showed neuronal activation (first A-B section of Figure 6c and Figure 6d). However, in comparisons within Silent 2, none of the pairs exhibited the same hemodynamic trends.

Out loud trials. In comparisons within Out Loud 1, Pairs 1, 2 and 3 all exhibited neuronal deactivation (first C-D sections of Figures 6a-6c). In comparisons within Out Loud 2, Pairs 1 and 3 both exhibited neuronal deactivation (second C-D sections of Figures 6a and 6c), and both children in Pair 4 exhibited an atypical trend (second C-D sections of Figure 6d).

Patterns of Hemodynamic Trends Across Trials and Within Conditions: Pair-by-pair Comparisons

Silent condition patterns. In pair-by-pair comparisons of patterns across trials in the silent condition, as shown in Table 6, two pairs exhibited the same pattern across Silent 1 and Silent 2, those being Pairs 1 and 4, who both showed a varying pattern of hemodynamic trends (i.e., one trend in the first trial and a different trend in the second trial) (A-B sections of graphs in Figure 6a and 6d).

Out loud condition patterns. In the out loud condition, two pairs exhibited the same pattern across trials, those being Pairs 1 and 3, who had consistent neuronal deactivation across Out Loud 1 and Out Loud 2 (C-D sections of graphs in Figure 6a and Figure 6c).

Group Patterns of Hemodynamic Trends Across Trials and Within Conditions

When comparing group patterns across trials within the silent condition, the majority of participants in both groups had different patterns of activation across Silent 1 and Silent 2 (Table 6), with no distinct similarities or differences between groups. In contrast, in the out loud condition, 3 of the 4 CWS (75%) had consistent neuronal deactivation across Out Loud 1 and Out Loud 2 (for example, CWS in Pair 1 in Table 6 and C-D sections of CWS 1 graph in Figure 6a), compared to 2 of the 4 matched controls (50%) (for example, TFC in Pair 3 in Table 6 and C-D sections of TFC

1 graph in Figure 6c). The remaining 2 matched controls had varied patterns of hemodynamic trends across the out loud trials.

CHAPTER 4: DISCUSSION

Introduction

The primary aim of this study was to determine the test-retest reliability of using fNIRS to measure changes in oxyhemoglobin (HbO_2), de-oxyhemoglobin (HHb), cerebral oxygenation (HbDiff) and regional cerebral blood volume (tHb) in school-aged children during silent and out loud reading. This study also examined cerebral hemodynamic responses in typically fluent school-aged children during silent and out loud reading conditions, as well as compared cerebral hemodynamic responses of stuttering children and matched controls during silent and out loud reading. As this was a pilot study of an exploratory nature, the following findings are preliminary. They provide insight into the suitability of fNIRS for research with stuttering and non-stuttering children, identify potential issues associated with this measurement modality, and establish a base for future research.

Reliability of fNIRS Measures in TFC

Test-retest reliability was evaluated according to the criteria proposed by Cichetti and Sparrow (1981) wherein values ≥ 0.75 are

indicative of excellent reliability, values of 0.59- 0.75 are indicative of good reliability, values of 0.40-0.58 are indicative of fair reliability and any values less than 0.40 are indicative of poor reliability. This evaluation criteria has been used in previous studies that have assessed test-retest reliability of fNIRS measures (Watanabe et al., 2003; Zhang et al., 2011).

Reliability of delta values. Bland-Altman plots for delta values showed good agreement between the trials for both silent and the out loud conditions. Not all variables and conditions had outliers, and those that did had one outlier each; the exception to this was HHb silent, which had two outliers. For delta values, ICCs for all variables in the out loud condition ranged from fair to excellent. However, in the silent condition, only HbO_2 and tHb showed fair test-retest reliability, while HHb and HbDiff measures were found to be unreliable. Upon examination of outliers, it was found that TFC 2 was a common outlier in HHb and HbDiff plots in the silent condition, as well as in the HHb plot in the out loud condition. TFC 15 was outlier for both HbO_2 and HbDiff in the out loud condition. The remaining outliers were different participants. When outliers were removed, test-retest reliability improved considerably for all variables and conditions except HHb silent, in which the ICC dropped out of range and remained indicative of unreliability. Overall, it was found that delta values with outliers removed were more reliable in the out loud than the silent condition, with all variables being reliable in the out loud condition. In the silent condition, HbO2, HbDiff and tHb with outliers removed were found to be reliable, while HHb was found to be unreliable.

Reliability of sigma values. Similar to delta values, ICCs of sigma values indicated that measures in the out loud condition were reliable for all variables, ranging from fair to excellent reliability. However, in the silent condition, while measures of HbO_2 and tHb were found to have moderate to excellent reliability, measures of HHb and HbDiff were again found to be unreliable. Upon examination of outliers, it was found that TFC 2 was again an outlier for the same variables and conditions as was the case with delta values (HHb silent and out loud, and HbDiff silent). The remaining 2 outliers were in tHb silent and out loud. When outliers were removed, ICCs improved for all variables and conditions. However, despite the fact that the ICC increased for HHb, it still remained below the recommended criterion for acceptable reliability. Overall, measures of all variables were reliable for both conditions, with the exception of HHb silent.

Previous Studies Using ICCs to Evaluate Test-Retest Reliability

At present, the reliability of fNIRS has not been widely established. Despite the existence of several studies confirming the validity of fNIRS use with children, none have addressed the reliability of its use in measuring alterations in prefrontal hemodynamic responses in school-aged children during reading. However, several studies have examined the reliability of changes in prefrontal hemodynamics using fNIRS in various adult populations (Bhambhani et al., 2006; Kakimoto et al., 2009; Kono et al. 2007; Plichta et al., 2006; Schecklmann et al., 2008; Watanabe et al., 2003; Zhang et

al., 2011). Due to the use of different populations, varying experimental protocols and brain regions of interest, as well as differing statistical methods of assessing test-retest reliability, a direct comparison of these results with those of the present study cannot be made. However, a few studies have used ICCs to assess test-retest reliability during verbal fluency tasks. For example, using multi-channel measurements, Watanabe et al. (2003) assessed test-retest reliability at an interval of 13-462 days using design fluency (i.e., invention of novel figures), verbal fluency (e.g., word generation) and forced hyperventilation tasks. Fair reliability was found during design fluency (0.42) and good reliability was found during both verbal fluency (0.87) and hyperventilation (0.65). Schecklmann et al. (2008) assessed the short-term (3 weeks) and long-term (53 weeks) test-retest reliability of HbO_2, HHb and tHb during a word-generation task and found that at the single-channel level, acceptable reliability was found only for HbO_2 between T1 and T2 (0.5)and for HbO_2 and HHb between T2 and T3 (0.52 and 0.5 respectively). Another study that used ICCs to assess reliability of changes in HbO_2 during a word generation task (Kakimoto et al., 2009) found that reliability ranged from unreliable to excellent (-0.14 to 0.77; mean of 0.43) for each channel at the single-channel level. Overall, the test-retest reliability found in the present study is comparable and, in some cases, better than that of previous studies.

Possible Factors Affecting Reliability in the Present Study

Despite the generally fair to excellent test-retest reliability found in the present study, especially with outliers removed, the test-retest reliability of some of the variables and conditions was not as desirable. There is some discrepancy among researchers regarding cutoff values for ICCs, particularly towards the lower end of values (Charter, 2003). Ideally, ICCs above 0.75 for all variables and conditions would have been preferred, so as to be more widely accepted as being indicative of good test-retest reliability. There are several factors that can affect reliability, some of which may account for some of the lower ICC values found in this study.

Sample size and outliers. Sample size and outliers are two important factors that can affect correlational analyses. It is more likely for extreme values to appear within smaller sample sizes because there is not adequate representation of the sampled population. With larger sample sizes, the effect of these extreme values is more balanced out by the rest of the data. For this reason, ICCs were calculated with outliers and without outliers.

The majority of outliers found in this sample appeared to be randomly occurring with no distinguishing participant characteristics that could explain their existence as outliers. It is assumed that these outliers were just part of the natural variability of the data. However, the most prevalent outlier was TFC 2, who appeared as an outlier for the same three variables and

conditions for both delta and sigma values, indicating the likely existence of a contributing factor. During the initial familiarization with the equipment and testing protocol, as well as brief conversations with the researcher, this child appeared to be more excitable than the others, which may explain why this child appeared as a frequent outlier.

Use of a single channel measurement. Similar to the present findings, previous studies using verbal fluency tasks have reported a wide range of ICC values, including negative (i.e., unreliable) values, when test-retest reliability was assessed at the single channel level (Kakimoto et al., 2009; Schecklmann et al., 2008). It is generally expected that there will be greater variability associated with the use of a single channel, due to extra-cranial contributions in the field of view (Hiraoka et al., 1993). In order to offset this inherent lower reliability, it is suggested that multiple measurements are necessary to obtain more reliable measures of cerebral hemodynamic changes (Perrey, 2008). Single measure ICCs deliver information about the reproducibility of a single measure, whereas average measure ICCs indicate the accuracy of the derived mean of the repeated measures (Johnstone et al., 2005). As the present study aimed to assess the reproducibility of a single measurement, single measures ICCs were reported. However, both single measure and average measure ICCs have been reported in previous studies (Plichta et al., 2006, Schecklmann, 2008). In future studies, it may be beneficial to take the average of multiple measurements when measuring at a single-channel level.

Practice effects. Repeated testing with the same task gives rise to the possibility of practice effects (Kono et al., 2007). Practice effects can manifest as increases and/or decreases in cortical activation. Although this is more the case with studies in which a practice block is part of the experimental design (e.g., Hempel et al., 2004), other studies have suggested that some of variability between test-retest measurements taken as little as a week apart can be attributed to practice effect. As practice effects are liable to carry over with small test-retest intervals (Kono et al., 2007), it is possible the second reading of the passage in the present study was susceptible to practice effects, as the test-retest interval was only 3 minutes.

Differences between reading conditions. Test-retest reliability was found to be better in the out loud condition than in the silent condition for both delta and sigma values, with the exception of sigma HbDiff and tHb, although the difference in ICCs between the two variables was small in the latter. This discrepancy between silent and out loud reading may be due to the nature of the tasks. While out loud reading is a readily observable behavior, silent reading is not. Although participants were instructed to read silently, there was no way to verify that participants were paying full attention to the task during both trials, or that the given instructions were followed consistently between trials. Previous research has also shown that children and youth may have different levels of comprehension when they read out loud compared to silently (Miller and Smith, 1990), with out loud reading being preferred as it is felt to best aid reading comprehension

(Alshumaimeri, 2011). Sentence comprehension has been found to produce significant activation in the inferior frontal areas (Binder et al., 1997; Booth et al., 1999). It is possible that greater comprehension during the out loud trials could have resulted in more consistency in variable concentrations between out loud trials.

Differences between hemodynamic variables. With regards to differences in test-retest reliability between variables in the present study, HHb was found to be less reliable than HbO_2. The only exception to this was for sigma values in the out loud condition, where ICCs for both hemodynamic variables were comparable. Previous studies have also found lower reliability in HHb at both the single-channel and cluster-wise levels (Plichta et al., 2006; Zhang et al., 2011). Changes in HHb have been found to not be uniform across participants, with significant changes being found in some participants but not others (Miyai et al., 2001; Watanabe et al., 2003). Possible reasons for lower HHb reliability can be that (a) HHb is more spatially localized than HbO_2 (e.g., in a cluster of channels, changes in HHb may be detected only in a few channels whereas changes in HbO_2 are detected in most channels) (Leff et al., 2010; Plichta et al., 2006); and (b) HHb is more affected by systemic changes in physiological parameters such as blood pressure, heart rate, and blood flow (Boas et al., 2004; Kono et al., 2007).

Summary

As hypothesized, test-retest reliability of hemodynamic variables (HbO_2, HHb, HbDiff and tHb) during reading conditions was found to be moderate to excellent, with the exception of HHb during silent reading, which was found to be unreliable. Therefore, the results of the present study suggest that fNIRS is a reliable tool for measuring changes in all cerebral hemodynamic variables in fluent school-aged children during out loud reading, and for measuring changes in cerebral HbO_2, HbDiff and tHb in fluent school-aged children during silent reading. Factors that may affect and account for differences in test-retest reliability are outliers, use of a single channel, practice effects, task differences between reading conditions, and differences in characteristics between hemodynamic variables.

Statistical Analysis of Differences Between Reading Tasks in TFC

Delta values. Results from a two-by-two repeated measures ANOVA for delta values suggested no significant differences between conditions or trials for any of the hemodynamic variables. No interaction effect was found for HbO_2, HHb or tHb, although the interaction effect for HbO_2 was almost significant (p=0.05). However, a significant interaction between condition and trial was found for HbDiff, such that participants exhibited higher delta values in T1 of the out loud condition compared to T2. HbDiff (i.e., cerebral oxygenation), is said to accompany brain activity, such that during neuronal activation there is an increase in cerebral oxygenation (Perrey, 2008;

Rostrup et al., 2005; Villringer & Chance, 1997). Therefore, the results suggest that that neuronal activation in the first trial of the out loud condition was of greater magnitude (i.e., greater maximal change from baseline) than that of the second trial. As the reading passage was novel to participants in T1, but not T2, it is possible that the relatively decreased activation in T2 was due to the familiarity of the task. As mentioned above, changes in cortical activation have been found with repeated testing (Jansma et al. 2001; Karni et al., 1995), although these studies were not conducted using fNIRS.

Sigma values. Results from a two-by-two repeated measures ANOVA for sigma values showed no significant interactions between condition and trial for any of the hemodynamic variables. No significant differences between conditions or trials were found for HbO_2, HbDiff or tHb. However, results showed that there was a significant difference between silent and out loud reading conditions for HHb, with sigma values being higher in the out loud condition than the silent condition. As HHb increases during deactivation, this increased HHb during out loud reading may suggest that TFC exhibit greater deactivation during out loud reading compared to silent reading. Another possibility is that, since HHb sigma values were found to be unreliable during silent reading, this difference between HHb during silent reading and out loud reading may be spurious.

Qualitative Analyses of Hemodynamic Variable Trends in TFC

In fNIRS literature, it is widely accepted that an increase in HbO_2 concentration along with a concomitant decrease in HHb concentration is indicative of neuronal activation. Conversely, an increase in HHb concentration along with a concomitant decrease in HbO_2 concentration is said to be indicative of neuronal deactivation (Villringer & Chance, 1997; Strangman et al. 2008). fNIRS graphs for each participant were examined and trends of neural activity during reading conditions were categorized as being representative of neuronal activation or deactivation. Also seen were trends that did not fit the conventional definitions of activation and deactivation. These were categorized as being atypical trends, and were characterized by similar increases and decreases in HbO_2 and HHb concentration. Simultaneous increases and decreases in HbO_2 and HHb have been said to reflect a movement artifact or changes in extra-cerebral blood flow (Obrig & Villringer, 2003). Patterns of trends across trials within conditions were then analyzed, and identified as showing consistent activation, consistent deactivation or a varying trend across trials.

Although it was hypothesized that TFC would show consistent activation during silent reading, a varying pattern of trends was most commonly seen , with over half of the TFC demonstrating this pattern across silent trials. However, within this varying pattern of trends, activation was the most common trend in T1 of the silent condition. Of interest, however,

was the hemodynamic response in the out loud condition, where the most commonly seen pattern was that of consistent neuronal deactivation across trials. Although this pattern was seen in less than half (47%) of the participants, it was still contrary to the hypothesis of this study, which posited that TFC would show neuronal activation in the out loud condition. Previous studies have highlighted the role of the left IFG in the cortical network involved in reading (Cornelissen et al., 2009; Fiez and Petersen, 1998; Salmelin et al., 2000; Turkeltaub et al., 2002), and activation in Broca's area of the left IFG has even been seen during silent reading (Kober et al., 2001). Furthermore, given the possible involvement of the IFG in articulatory processes involved in out loud reading (Price et al., 1994), it was thought that neuronal activation would be more prevalent in the out loud condition.

A possible reason for this could be that although the left IFG is activated during the process of reading, it is not the primary or only region involved. In a meta-analysis of single-word oral reading, Fiez and Petersen (1998) identified common activation during reading in the left IFG, SMA, anterior cingulate cortex, bilateral motor and superior temporal cortex, left extrastriate cortex and bilateral and midline cerebellum. In a study of silent reading (mouthing the words) and out loud reading, Price et al. (1996) found that regions activated during reading were (a) visual and visual association areas, (b) motor, premotor and cerebellar areas, (c) temporoparietal areas, (d) prefrontal areas, and (e) subcortical areas. In comparing silent reading to out loud reading, they found that the only differences in activated regions

that occurred were restricted to sound generation and the response of the auditory cortex to the sound of the participant's voice during out loud reading. However, there is variability in the literature as to the cognitive processes and activated brain regions during reading (Turkeltaub et al., 2001), which can be due to participant factors or differences in tasks used. For example, while the present study used whole passages, many previous reading studies with typically fluent and/or stuttering speakers have used single-word reading tasks (e.g. Price et al., 1994; Salmelin et al., 2000; Turkeltaub et al., 2002).

There are also functional differences between adults and children in the processing of the same task. Schlagger et al. (2002) found age-related differences in word-processing in the left dorsal frontal region, suggesting that this region is immature in children; in the absence of activation in this region, the child's brain "adopts an alternative strategy" (pg. 1479) that includes greater use of other regions, such as the left extrastriate region. It is possible that immaturity of the prefrontal region in children may account for the several instances of atypical trends seen during both silent and out loud reading. Given that the present study used a single-channel measurement, it was not possible to examine hemodynamic responses in other brain regions involved in reading and pinpoint differences in regions of activation between participants. Further studies using multiple-channel fNIRS measurements will provide a better understanding of the areas activated during reading and differences between silent and out loud reading in children.

Qualitative Analyses of Hemodynamic Variables in CWS and Matched Controls

Hemodynamic variable trends and patterns in CWS were categorized as mentioned above. Pair-by-pair comparisons within trials showed that the greatest similarities within pairs occurred during the first trial of each conditions, with the children in 3 of the 4 pairs exhibiting identical trends in T1 of both the silent and the out loud condition. When examining patterns of hemodynamic trends, two pairs in the silent condition exhibited the same varying pattern across trials. In the out loud condition, two pairs exhibited the same pattern of consistent deactivation. Given the small sample size of these groups, it is difficult to draw conclusions from these results. However, similarities were present within the majority of pairs in the first trial of each condition, and in half of the pairs across trials within conditions. This suggests the possibility that, in this age range, differences in hemodynamic trend patterns in the left IFG between CWS and TFC during reading may not be so pronounced. As the mean %SS in this study was lower than that used in some other studies (e.g., Chang et al., 2008; Ingham et al., 2012; and Sato et al., 2011), it is possible that the stuttering severity of the CWS was not enough to elicit an observable difference in cerebral hemodynamic trends within pairs. Certainly, future studies with larger sample sizes will provide more insight into potential similarities and differences.

Contrary to the hypothesized neuronal activation during silent reading, when comparing hemodynamic patterns between groups, no distinct similarities or differences were noted in the silent condition. However, as hypothesized, during the out loud condition, 75% (3 of 4) CWS exhibited consistent neuronal deactivation, compared to 50% (2 of 4) TFC. While this is not in itself conclusive given the very small sample size, and the fact that many of the 15 TFC also exhibited consistent deactivation during out loud reading, it does suggests the possibility that CWS have decreased neuronal activity in the left IFG during out loud reading compared to matched TFC. Hypoactivity in the left pre-frontal region of stuttering adults compared to fluent speakers has been well documented. Wu et al. (1995) found decreased activity in the left IFG of stuttering speakers during oral reading compared to fluency-induced choral reading, as well as compared to fluent speakers. Overt speech has been shown to produce weaker activation in left hemispheric pre-frontal speech regions in stuttering speakers compared to fluent speakers, as well as increased activation in the right hemisphere homologues of these regions (e.g., IFG and middle frontal gyrus) which are thought to be related to atypical planning in stuttering speakers (De Nil et al. 2008; Lu et al., 2009; Lu et al., 2010). Additionally, stuttering adults exhibit significant left frontal activation in Broca's area (pars opercularis and pars triangularis of the left IFG) during silent reading and increased right hemisphere activation during oral reading (De Nil et al., 2000). This, along with abnormal neuroanatomy in the form of grey matter deficits in this region that are present in both adults

and children who stutter, provide increasing evidence that suggests that this area is related to the cause of stuttering (Chang et al., 2008; Kell et al., 2009; Watkins et al., 2008). However, studies comparing left prefrontal activity in CWS and TFC have not been conducted, therefore a direct comparison to the results of the present study cannot be made.

Although the findings of the present study do not provide support for the findings the abovementioned studies, they do suggest some minor differences between CWS and TFC groups. At minimum, they highlight the importance of conducting future qualitative and quantitative analyses of cerebral hemodynamic differences during reading between CWS and TFC.

Study Limitations

Lack of audio data. Due to technical issues, audio recordings of the fNIRS sessions were not available, thus preventing analysis of CWS stuttering frequency (%SS) during the out loud reading passage. Although most of the CWS (3 of 4) underwent the fNIRS session approximately one week following their pre-treatment assessment, stuttering frequency data during the out loud reading may have shed light on hemodynamic responses of CWS during the task. It also prevents the matching of stuttering syllables to points on the fNIRS graphs, thereby eliminating a valuable avenue of analysis.

Stuttering severity. Mean stuttering severity of the CWS group was 2.39 (median: 2.03 %SS, range: 1.0-4.5% SS). Some of the children in the present study had %SS that was lower than that found in previous studies

that have generally studied groups of stuttering individuals with %SS range of approximately 2-5% (e.g., Chang et al., 2008; Ingham et al., 2012; Sato et al., 2011). Due to the extreme difficulty in recruiting stuttering children with no concomitant issues, it was not possible to further restrict recruitment parameters so as to obtain children who stuttered more severely. It is possible that having a group of CWS with milder stuttering severity could have influenced the results of this study, as stuttering severity has been previously found to positively correlate with neural activity in areas such as the basal ganglia and negatively correlate with neural activity in areas such as the supplementary motor area (Giraud et al., 2007; Ingham et al., 2012).

Gender imbalance. Another limitation was the gender imbalance in the TFC group (female=12; male=3). Despite rigorous recruitment efforts over a six-month period, it was difficult to find children who were willing to participate in the study. For example, although 170+ recruitment packages were distributed within the school, only 16 responses were received. It so happened that the majority of respondents were female. Additionally, a few male respondents were not able to participate as a result of failing the screening tests. Further recruitment efforts using snowballing techniques and purposive sampling also did not result in an ideal male to female ratio. Due to time constraints, as well as the low response rate to employed recruitment strategies, it was not possible to wait until more male TFC could be recruited. Although having a primarily female sample may have made the present findings less susceptible to the impact of sex differences in cerebral

organization of reading-related processes (Pugh et al., 1996; Shaywitz et al., 1995), it also makes these findings less generalizable to the population of TFC school-aged children at large.

fNIRS limitations. As mentioned above, a single-channel measurement is not as desirable as it has been found to be less reliable than multi-channel measurements. There is also the inherent limitation of fNIRS not being able to quantitatively measure hemoglobin concentration in cerebral tissue separately from that in extra-cerebral tissue, particularly in the case of continuous-wave (CW) instruments such as that used in the present study. For example, changes in skin blood flow have been shown to influence fNIRS signals both during rest and activation. CW instruments provide only a relative measure of changes in hemoglobin concentrations, thereby preventing quantification of hemoglobin concentration changes. These are central issues that place limitations on fNIRS use and prevent it from being used as a stand-alone tool (Dieters et al., 2011; Murkin and Arango, 2009; Hoshi, 2011). Next generation fNIRS methods that are capable of selectively and quantitatively measuring cerebral hemoglobin are being developed.

Methodological issues. Theoretically, when determining test-retest reliability, tasks and task conditions should be identical. However, in the present study, although the passages and tasks were identical, the first reading was a novel one, while the second reading was not. In future studies,

it may be beneficial to increase the duration between test and retest sessions, so as to reduce potential practice effects and improve test-retest reliability. Previous studies have separated test and retest sessions from one week up to a year, and longer intervals between consecutive trials have been shown to result in increased test-retest reliability (Kono et al., 2007; Schecklmann et al., 2008). Due to the limited time frame allotted for the completion of this study, this was not possible in the present study.

Directions for Future Research

As this study explores avenues of brain imaging research that are relatively novel – those being the reliability of fNIRS use with children who do and do not stutter during reading, as well as comparative analyses of cerebral hemodynamic responses during reading in stuttering and non-stuttering children using fNIRS – the findings of this study serve only as a basis for future research. Given that only a very small sample of CWS were studied, as well as the gender imbalance in the TFC group, further research with sufficiently large and balanced groups of CWS and matched TFC should be undertaken. Such studies would more powerfully assess the test-retest reliability of fNIRS measures of prefrontal hemodynamic changes in stuttering children. They would also help determine whether the differences in hemodynamic trends and patterns of trends seen between TFC and CWS in the present study are attributable to stuttering pathology or are due to an unrelated factor(s).

With regards to the limitations of the present study, future research including within-task %SS for CWS during out loud reading would be very valuable. This information would provide a more thorough, time-relevant interpretation of cerebral hemodynamic responses and would help determine whether %SS during the task is a contributing factor in individual activation differences. Additionally, including syllable rate as a factor would be beneficial, as previous studies have found syllable rate to influence neural activation and BOLD responses, making it a potential source of activation differences between stuttering and fluent speakers. For example, brain activity in regions such as the middle frontal gyrus in people who stutter and the superior temporal gyrus in fluent speakers has been found to be positively correlated with syllable rate. Activity in other regions, such as the thalamus in people who stutter, and the supplementary motor area in fluent speakers, has been found to negatively correlate with syllable rate (Ingham et al., 2012; Riecker, Wildgruber, Dogil, Grodd, & Ackermann, 2002; Riecker, Kassubek, Groschel & Grodd, 2006).

Questions regarding the lower reliability during silent reading, the ideal test-retest interval between trials, ideal duration of the baseline period and individual activation differences could also be addressed in future research.

Conclusion

To date, little research has been conducted using fNIRS with school-aged children, and even less still with children who stutter. This study provides support for the use of fNIRS with both typically fluent and stuttering school-aged children, and demonstrates that fNIRS is a reliable tool for measuring changes in prefrontal cerebral hemodynamics in typically fluent children during out loud reading, and hemodynamic changes in HbO2, HbDiff and tHb during silent reading. Therefore, it appears promising that fNIRS may be a reliable method of brain imaging with stuttering children during reading, particularly out loud reading. The findings of this preliminary study also bring to attention differences in hemodynamic trend patterns between children who do and do not stutter during reading, particularly the consistent deactivation during out loud reading that was seen more in CWS than matched controls. Although these results are preliminary, they underscore the importance and value of conducting future research with CWS, who are closer to the age of onset of stuttering and exhibit less confounding compensatory effects of stuttering. By conducting such research, it will become clearer which neural correlates of stuttering are compensatory and which are tied to the underlying causes of stuttering. With this knowledge, we will be better able to inform clinical practices and understand treatment outcomes.

Table 1

Hemodynamic Variable Trends in TFC

Participant	Silent 1			Silent 2			Out Loud 1			Out Loud 2		
1	activation			activation			deactivation			deactivation		
2	deactivation			atypical			deactivation			deactivation		
3	atypical			atypical			atypical			atypical		
4	deactivation			atypical			deactivation			atypical		
5	activation			deactivation			activation			activation		
6	activation			activation			activation			activation		
7	activation			activation			activation			deactivation		
8	atypical			atypical			deactivation			deactivation		
9	atypical			activation			deactivation			deactivation		
10	atypical			atypical			deactivation			atypical		
11	atypical			deactivation			deactivation			deactivation		
12	activation			atypical			atypical			atypical		
13	deactivation			atypical			atypical			atypical		
14	activation			activation			deactivation			deactivation		
15	deactivation			atypical			deactivation			deactivation		
	A	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**
TOTAL	6	4	5	5	2	8	3	9	3	2	8	5

Note. A = Activation; D = Deactivation; AT = Atypical

Table 2

TFC Means and Standard deviations (SD) of Delta and Sigma Values

	Silent 1		Silent 2		Out Loud 1		Out Loud 2	
Variable	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Δ HbO_2	0.59	0.76	0.79	0.69	1.80	2.18	1.04	1.49
Δ HHb	-0.28	0.41	-0.37	1.85	-0.35	0.75	-0.23	0.40
Δ HbDiff	0.51	0.75	0.93	1.19	1.73*[a]	1.89	0.69*[a]	1.08
Δ tHb	0.92	1.01	0.90	1.60	1.24	2.86	1.62	2.26
Σ HbO_2	-141.60	880.80	78.43	436.70	94.58	939.90	16.48	690.54
Σ HHb	81.43*[b]	192.66	-100.90*[b]	581.70	288.34*[b]	553.23	252.83*[b]	368.44
Σ HbDiff	-223.03	979.90	179.33	402.46	74.37	1060.72	-235.35	656.41
Σ tHb	-60.16	815.88	-22.42	946.73	382.91	1134.96	270.31	891.23

*p<.05

[a]Mean delta value for Out Loud 1 was significantly higher than the mean delta value for Out Loud 2.

[b]Out loud condition means were significantly higher than silent condition means (main effect of condition).

Table 3

Summary of Intra-class Correlation Coefficients for TFC

Variable	**Silent (delta)**	**Out Loud (delta)**	**Silent (sigma)**	**Out Loud (sigma)**
HbO_2	.45*	.69*	.64*	.71*
		(.87*)		
HHb	.01	.63*	Out of range	.57*
	(out of range)	(.75*)	(.26)	(.74*)
HbDiff	out of range	.53*	Out of range	.45*
	(.53*)	(.64*)	(.67*)	
tHb	.53*	.84*	.92*	.88*
		(.93*)	(.94*)	(.91*)

** p<0.05.*

Note. ICCs with outliers removed are shown in brackets.

Table 4

Summary of ANOVA for TFC Delta Values

Variable		Condition	Trial	Condition x Trial
HbO_2	*F*	2.31	1.93	4.5*
	p	.15	.19	.05
	ηp^2			0.24
HHb	*F*	0.20	0.01	0.13
	p	.89	.94	.73
	ηp^2			
HbDiff	*F*	1.43	1.32	7.36*
	p	.25	.27	.02
	ηp^2			.35
tHb	*F*	0.66	0.55	0.57
	p	.43	.47	.46
	ηp^2			

* p < .05.

Note. df (1,14) for all groups.

Table 5

Summary of ANOVA for TFC Sigma Values

Variable		Condition	Trial	Condition x Trial
HbO_2	*F*	0.184	0.53	1.46
	p	.68	.48	.25
	ηp^2			
HHb	*F*	8.45	2.7	0.31
	p	.01*	.12	.59
	ηp^2	0.15		
HbDiff	*F*	0.08	0.10	2.29
	p	.78	.76	.15
	ηp^2			
tHb	*F*	1.91	0.25	0.77
	p	.19	.63	.39
	ηp^2			

* $p < .05$.

Note. df (1,14) for all groups.

Table 6

Hemodynamic variable trends for CWS and matched TFC

CWS – TFC pair	**Silent 1**				**Silent 2**				**Out Loud 1**				**Out Loud 2**			
	CWS		**TFC**		**CWS**		**TFC**		**CWS**		**TFC**		**CWS**		**TFC**	
1 *CWS 1 & TFC 2*	activation		deactivation		deactivation		atypical		deactivation		deactivation		deactivation		deactivation	
2 *CWS 2 & TFC 4*	deactivation		deactivation		deactivation		atypical		deactivation		deactivation		deactivation		atypical	
3 *CWS 3 & TFC 1*	activation		activation		deactivation		activation		deactivation		deactivation		deactivation		deactivation	
4 *CWS 4 & TFC 12*	activation		activation		deactivation		atypical		deactivation		atypical		atypical		atypical	
	A	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**	**A**	**D**	**AT**
TOTAL	3	1	0	2	2	0	0	4	0	1	0	3	0	4	0	0	3	1	0	3	1	0	2	2

Note. A = Activation; D = Deactivation; AT = Atypical.

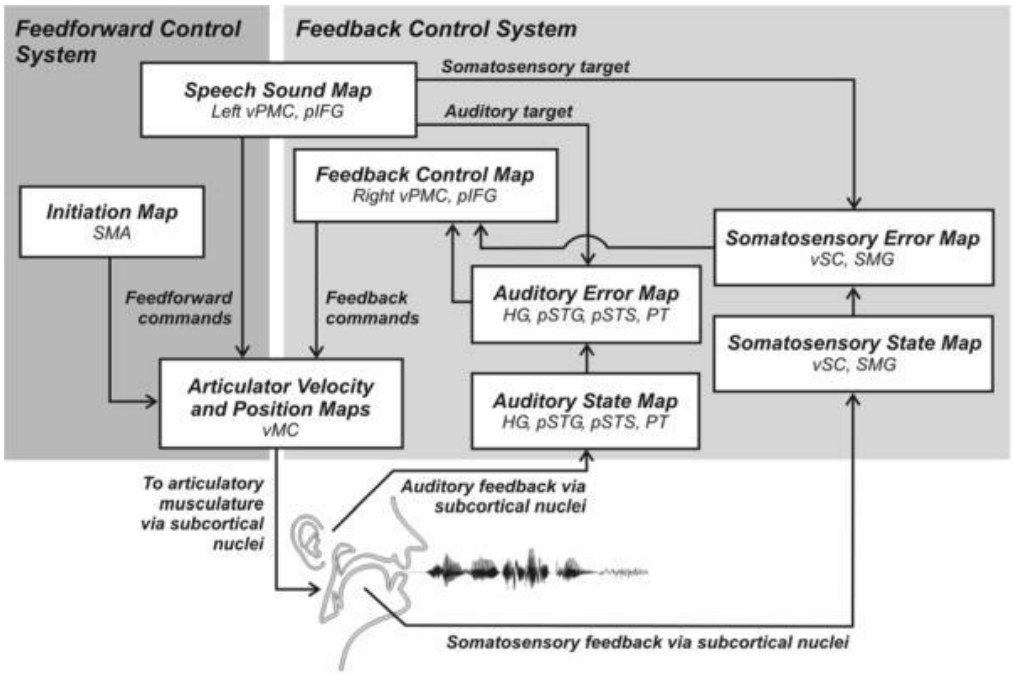


Figure 1. Neural processing stages of the Directions into the Velocities of Articulators (DIVA) model of speech production and neural substrates hypothesized to correspond with each component of the model (Guenther et al., 2006). [1]

[1] Reprinted from Elsevier, Vol. 25, Guenther , F.H and Vladusich, 2012, A neural theory of speech acquisition and production, Pages No. 408, Copyright (2012), with permission from Elsevier.

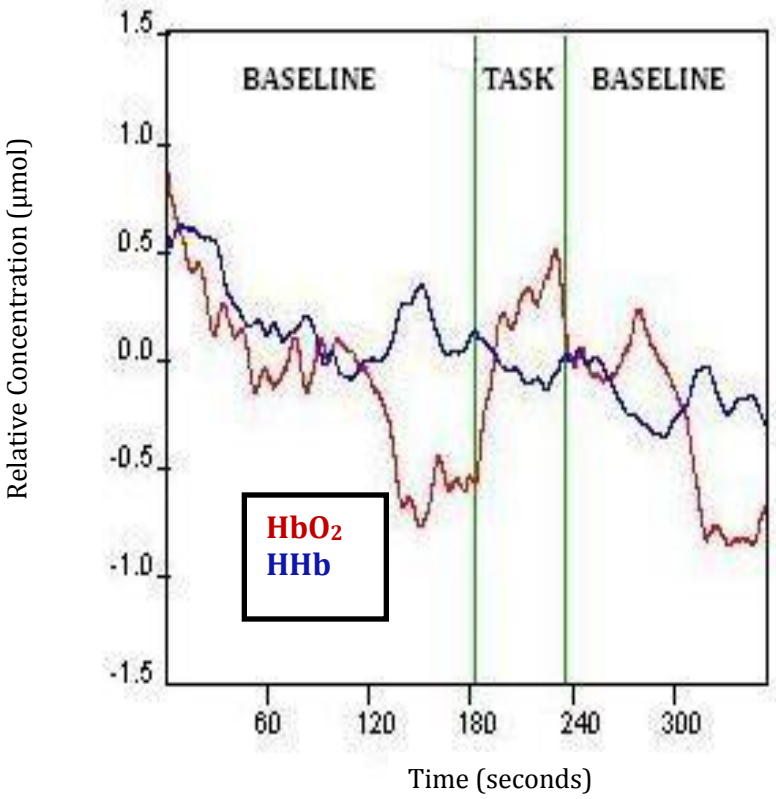


Figure 2a. Representative graph depicting neuronal activation during the task. Neuronal activation is conventionally defined as an increase in HbO_2 and a concomitant decrease in HHb, as depicted above.

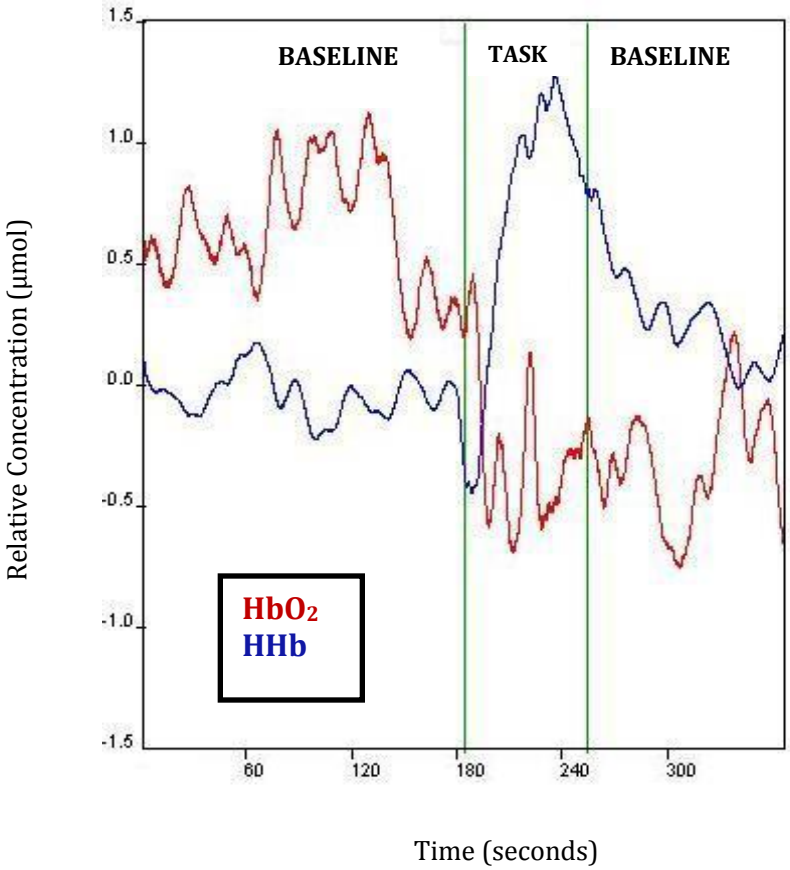


Figure 2b. Representative graph depicting neuronal deactivation. Neuronal deactivation is conventionally defined as a decrease in HbO_2 along with a concomitant increase in HHb, as depicted above.

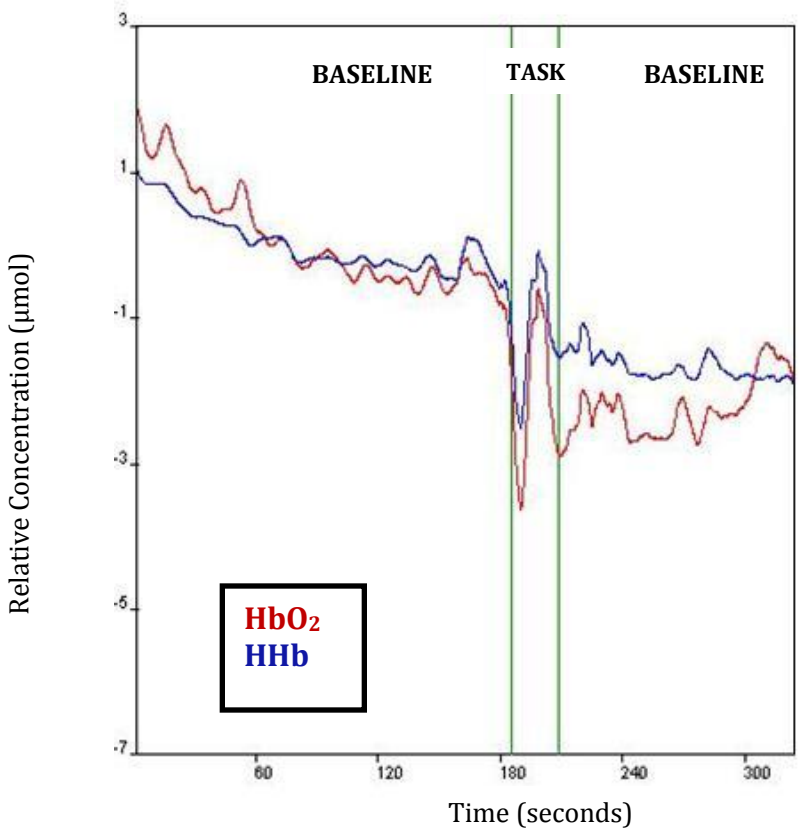


Figure 2c. Representative graph depicting an atypical hemodynamic trend during the task. The similar incline and decline of the HbO_2 and HHb traces are indicative of an atypical pattern that cannot be classified as either neuronal activation or deactivation.

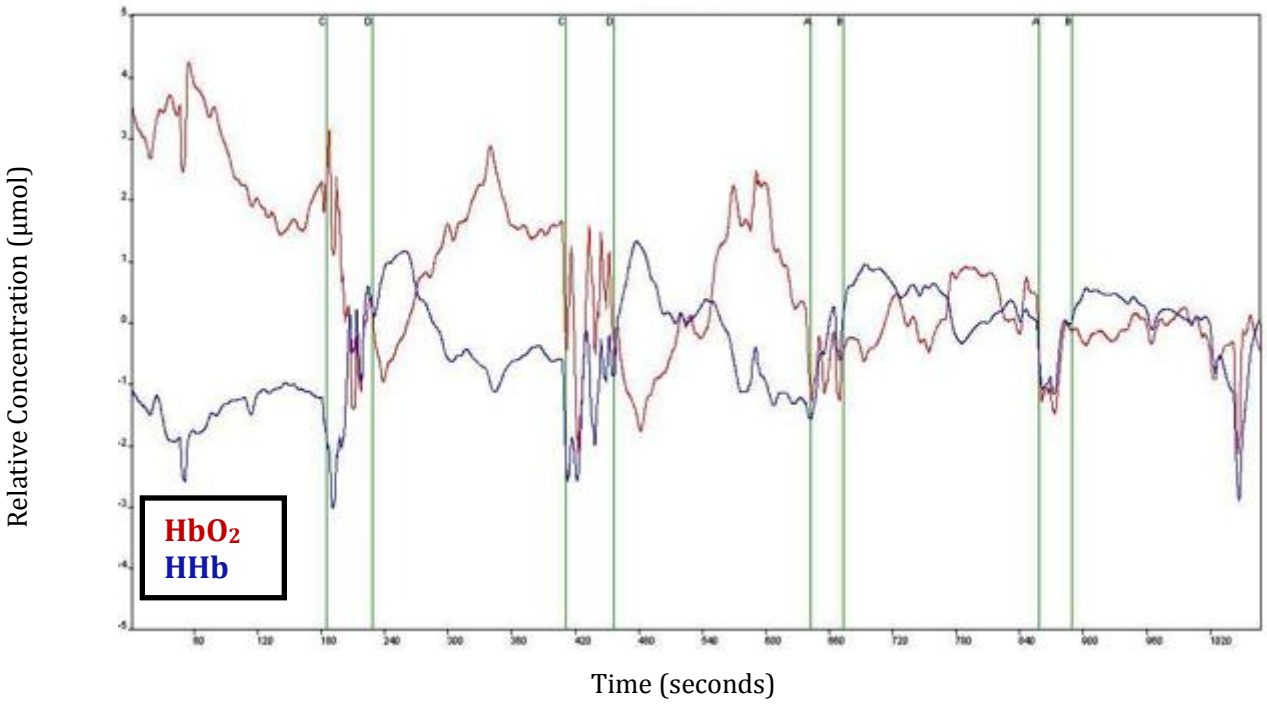


Figure 3a. Representative example of a varying pattern in both the silent condition task (A-B sections) and the out loud condition task (C-D sections).

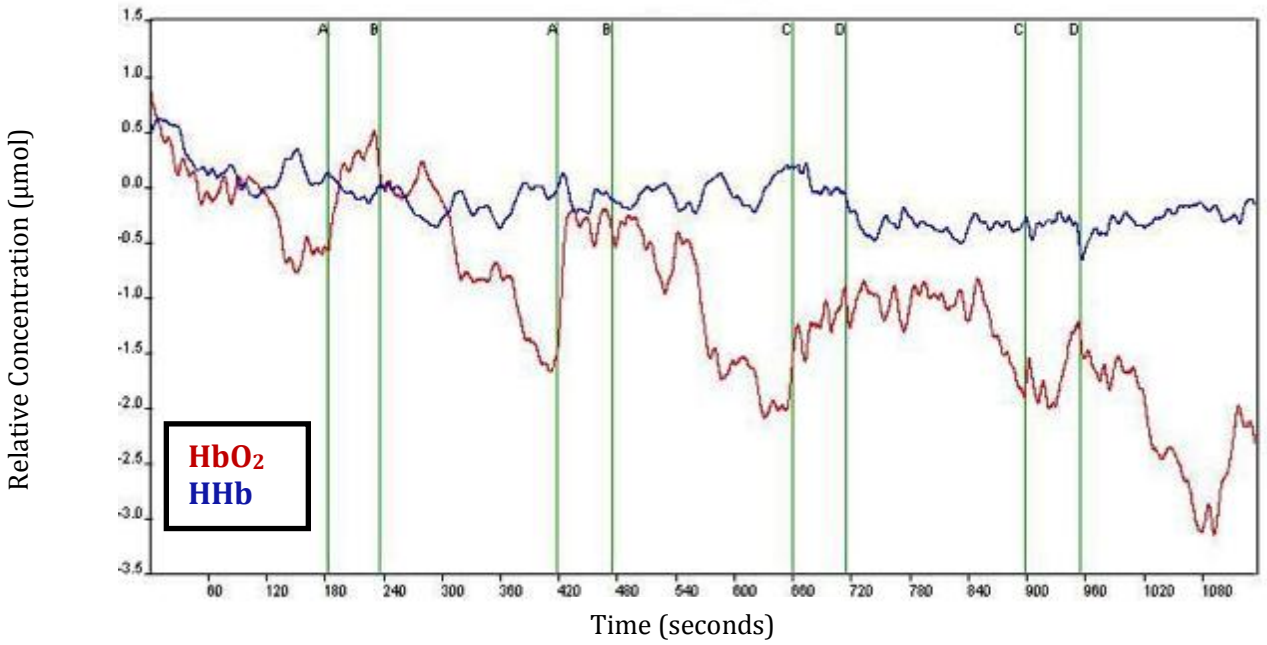


Figure 3b. Representative example of consistent activation in the silent condition task (A-B sections).

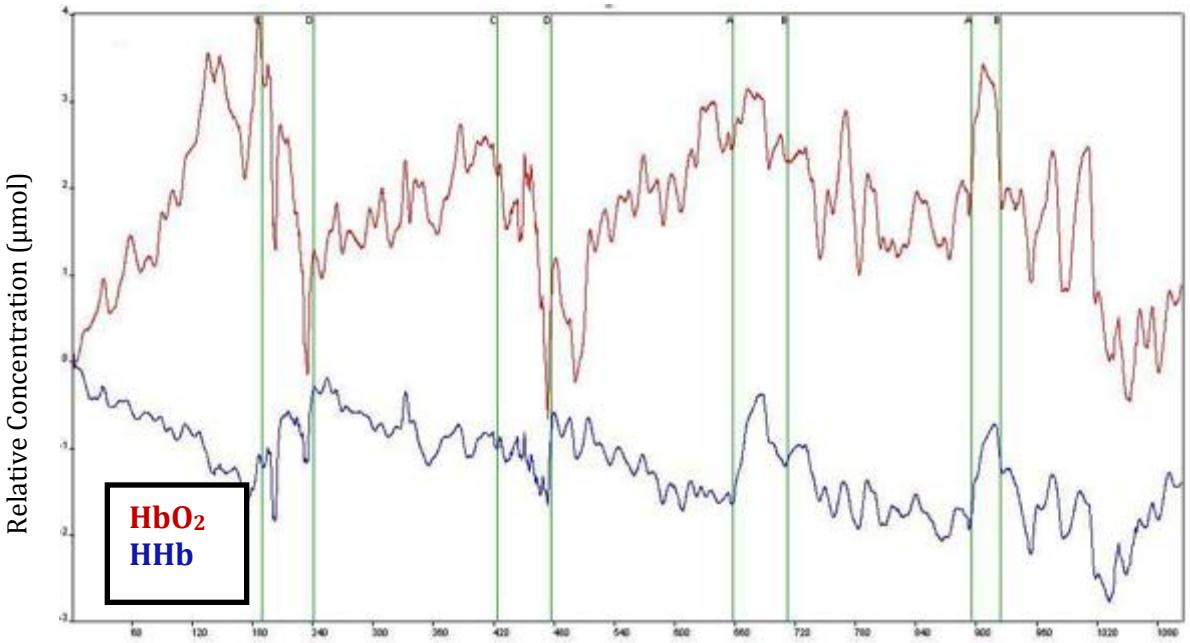


Figure 3c. Representative example of a consistent atypical trend in the silent condition (A-B sections).

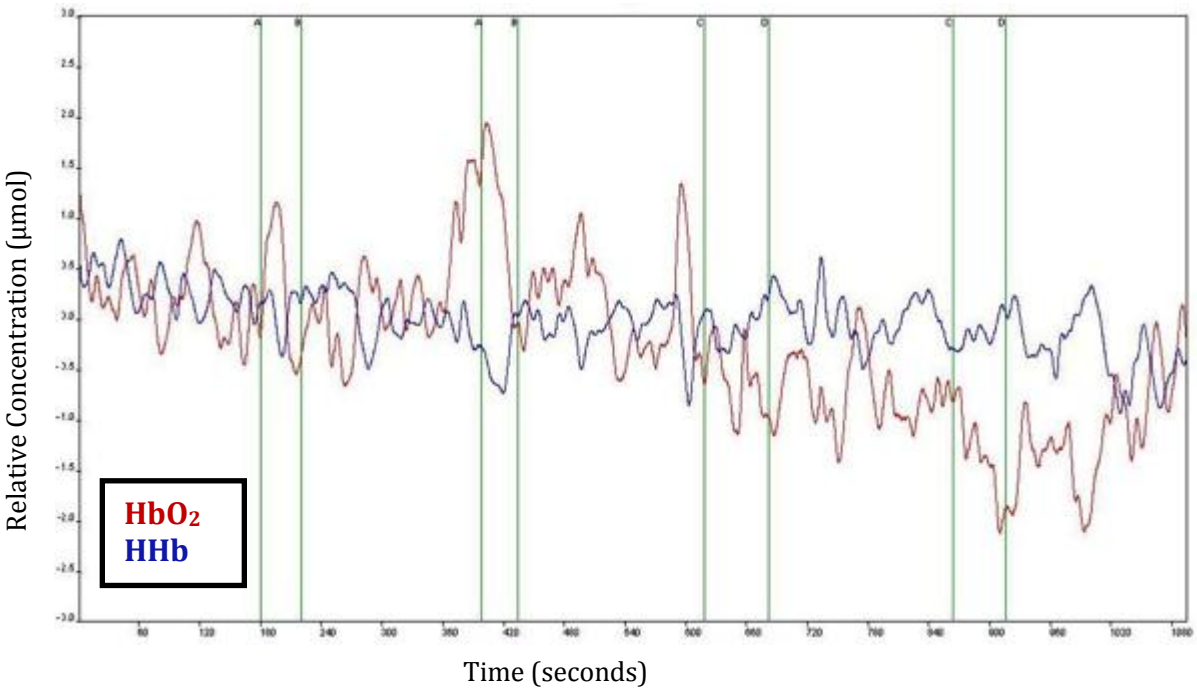


Figure 3d. Representative example of consistent deactivation in the out loud condition (C-D sections).

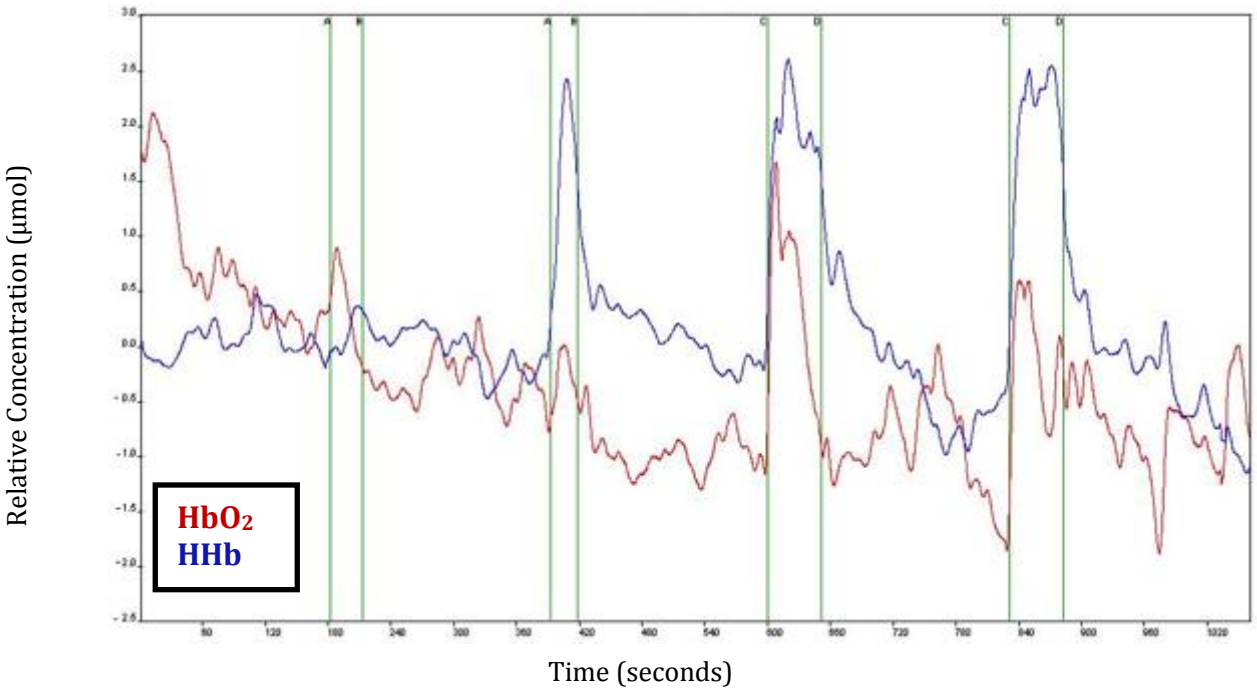


Figure 3e. Representative example of a consistent atypical trend in the out loud condition (C-D sections).

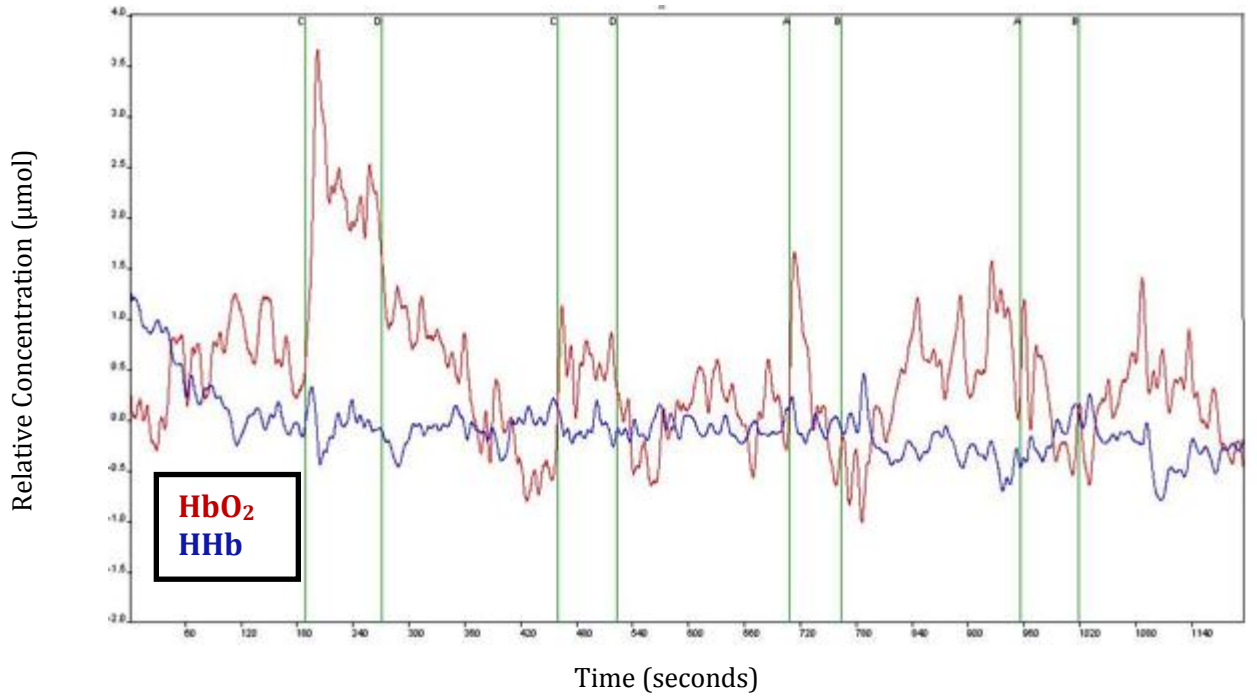


Figure 3f. Representative example of consistent activation in the out loud condition (C-D sections).

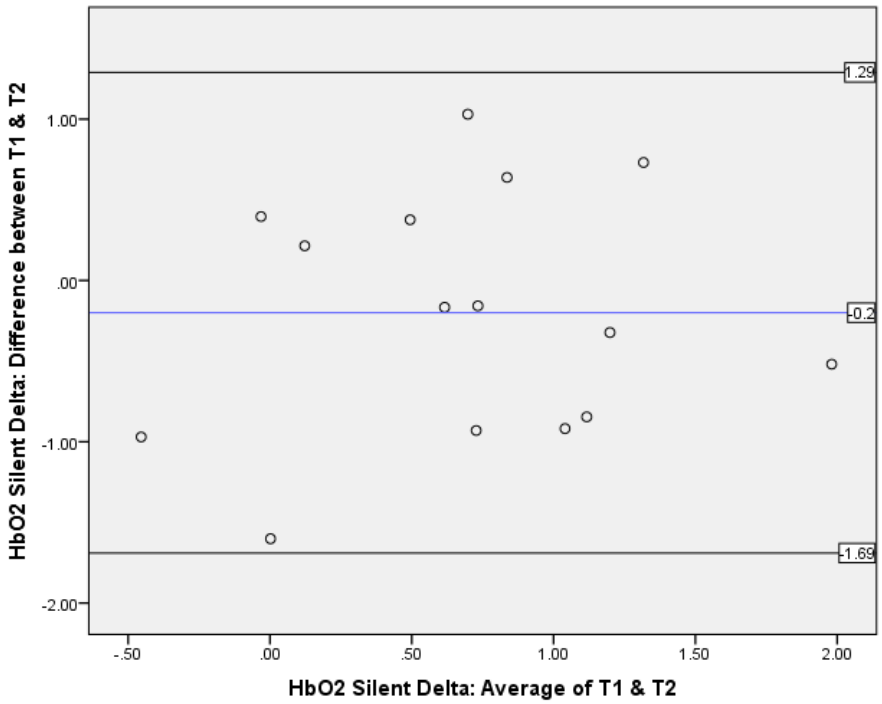


Figure 4a. Bland-Altman plot for HbO_2 silent delta values in TFC. There were no outliers. The ICC of the two trials was .45.

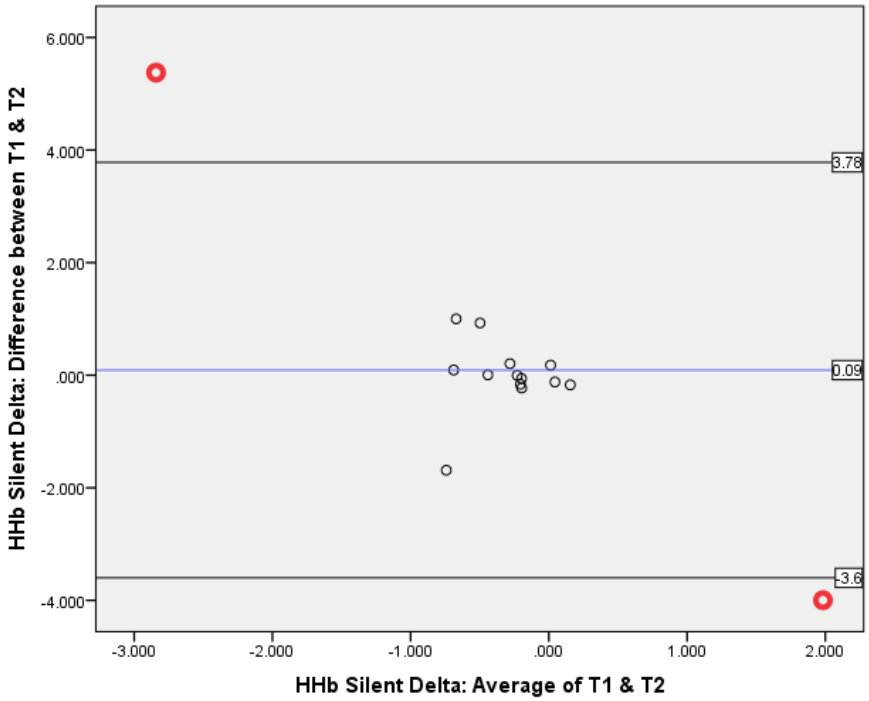


Figure 4b. Bland-Altman plot for HHb silent delta values in TFC. There were two outliers, which are indicated in bold red. The ICC of the two trials was .01.

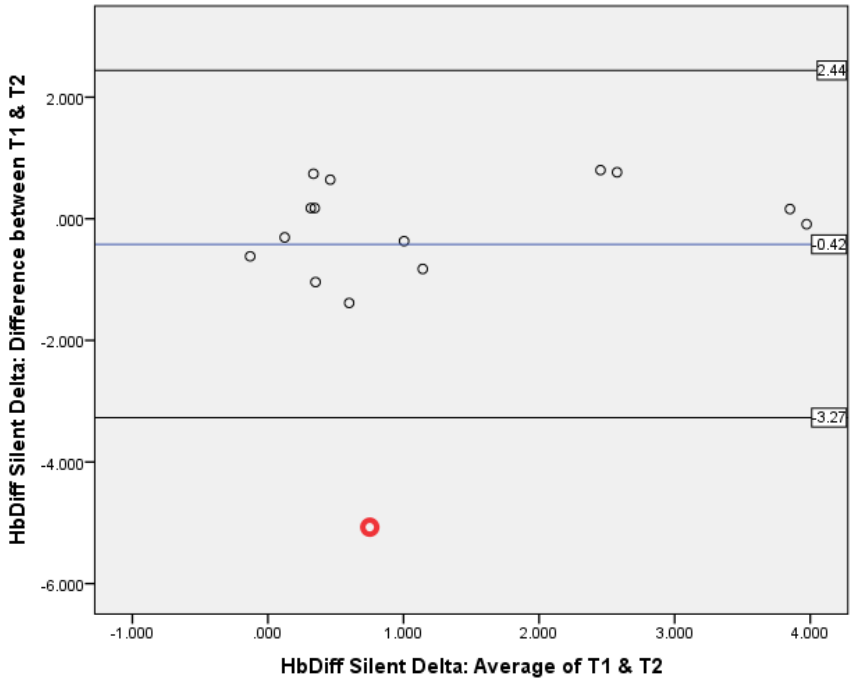


Figure 4c. Bland-Altman plot for HbDiff silent delta values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was out of range.

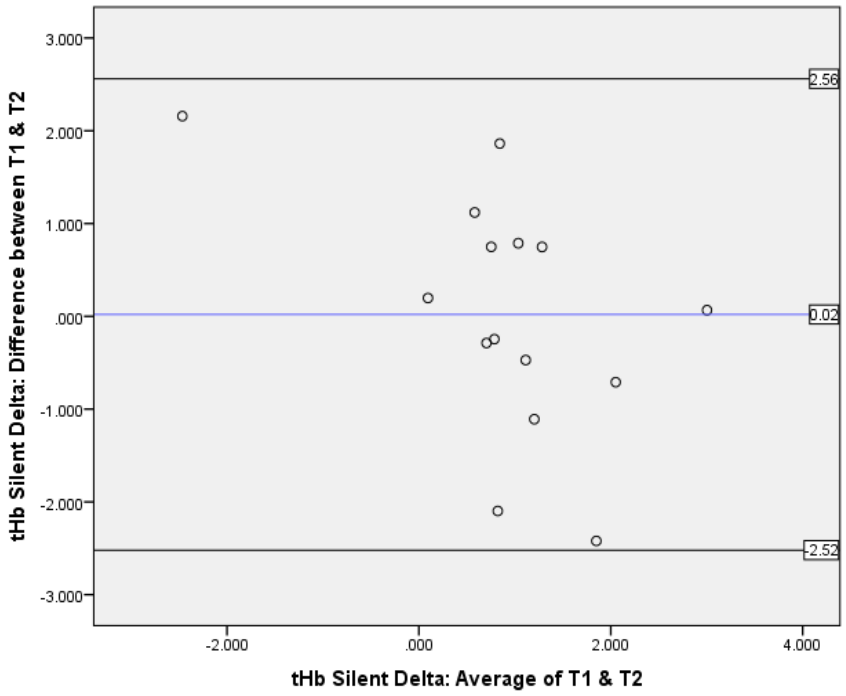


Figure 4d. Bland-Altman plot for tHb silent delta values in TFC. There were no outliers. The ICC of the two trials was .53.

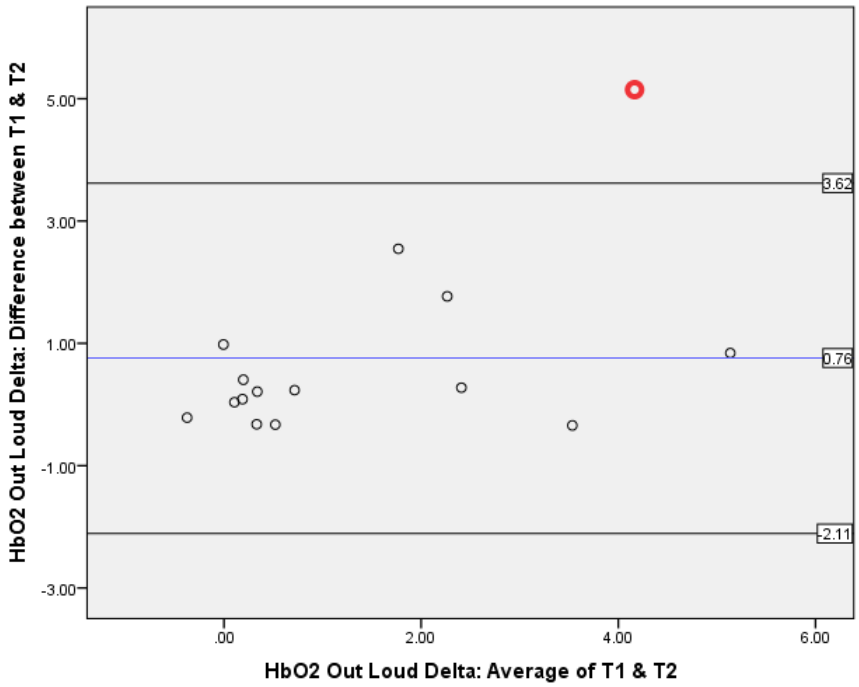


Figure 4e. Bland-Altman plot for HbO_2 out loud delta values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .69.

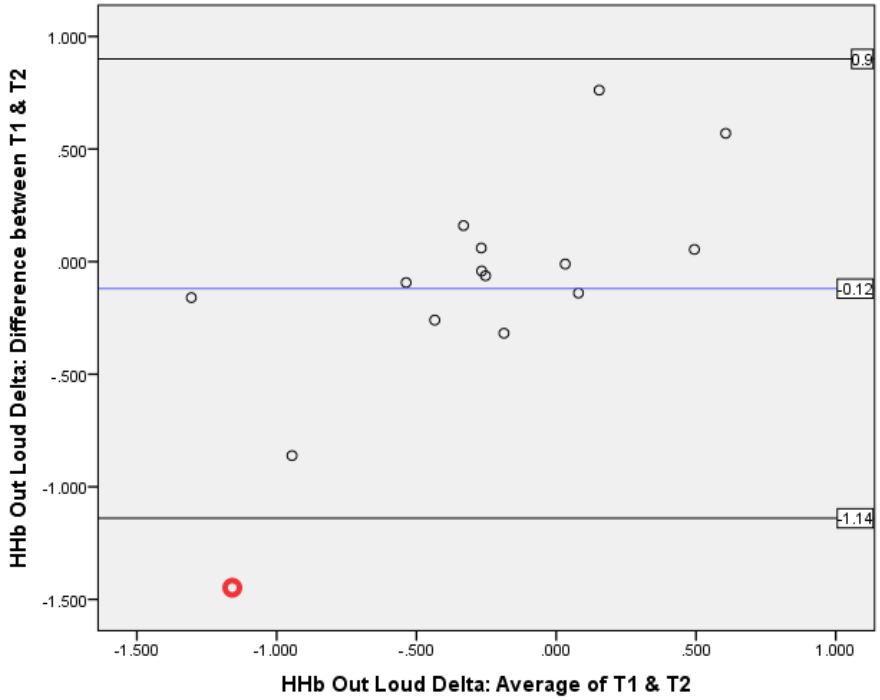


Figure 4f. Bland-Altman plot for HHb out loud delta values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .63.

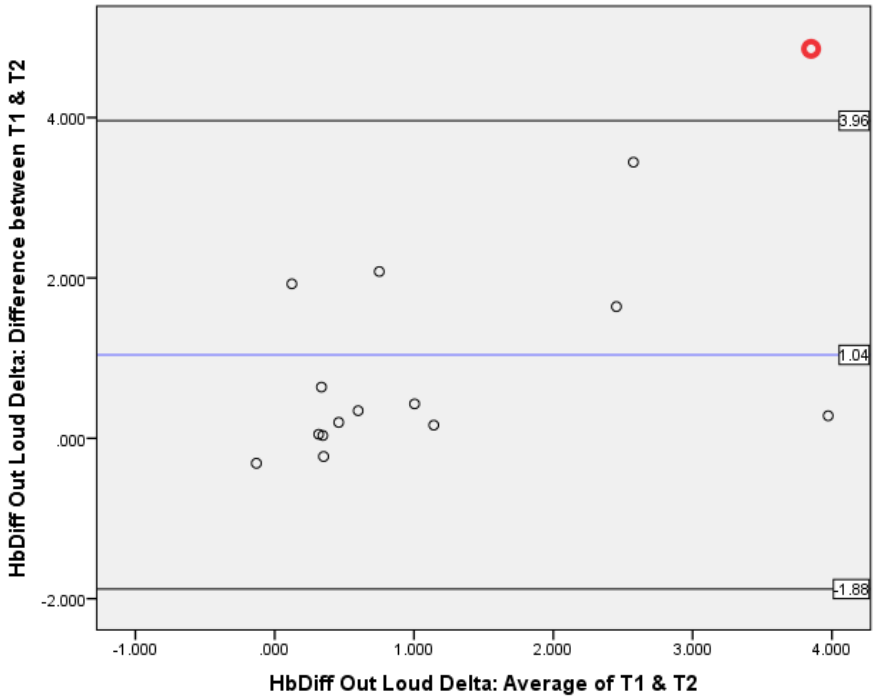


Figure 4g. Bland-Altman plot for HbDiff out loud delta values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .53.

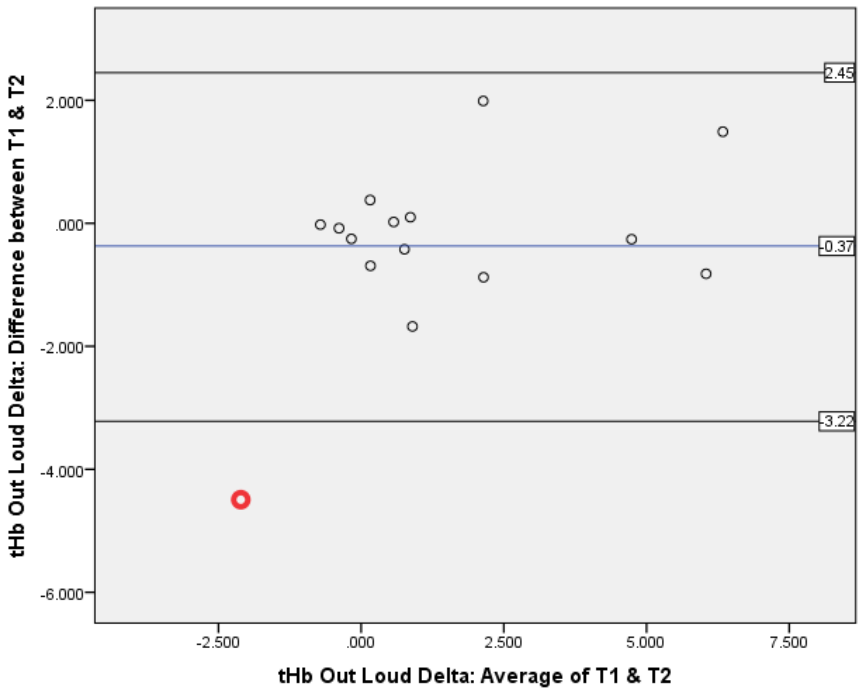


Figure 4h. Bland-Altman plot for tHb out loud delta values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .84.

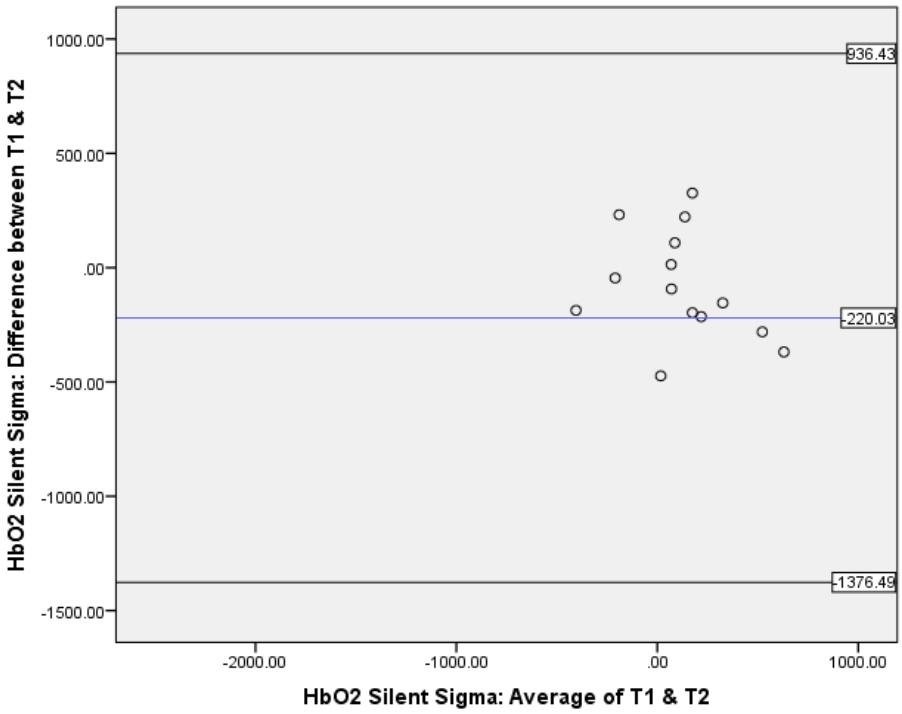


Figure 5a. Bland-Altman plot for HbO_2 silent sigma values in TFC. There were no outliers. The ICC of the two trials was .64.

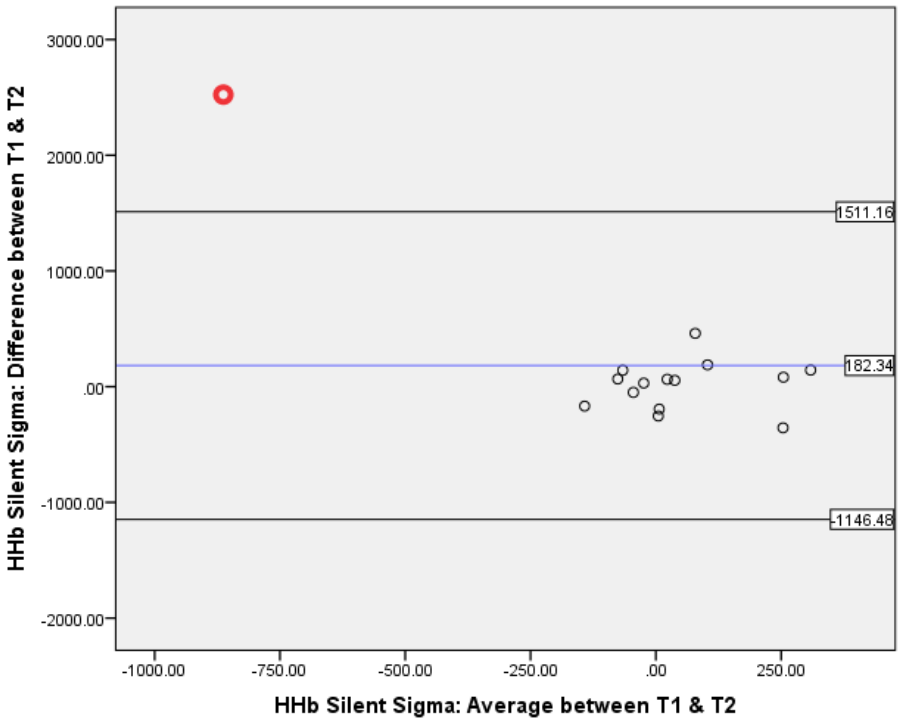


Figure 5b. Bland-Altman plot for HHb silent sigma values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was out of range.

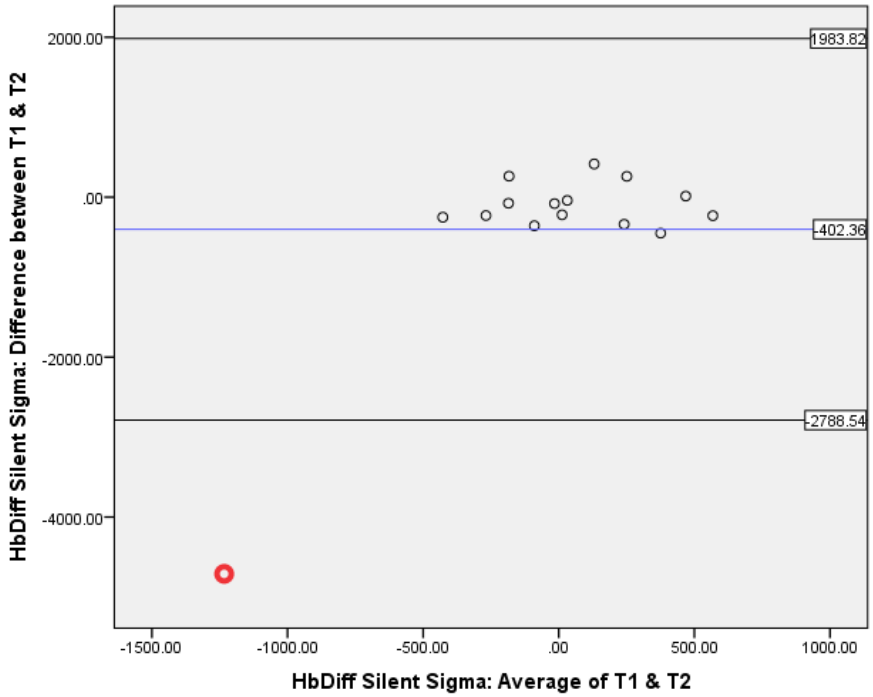


Figure 5c. Bland-Altman plot for HbDiff silent sigma values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was out of range.

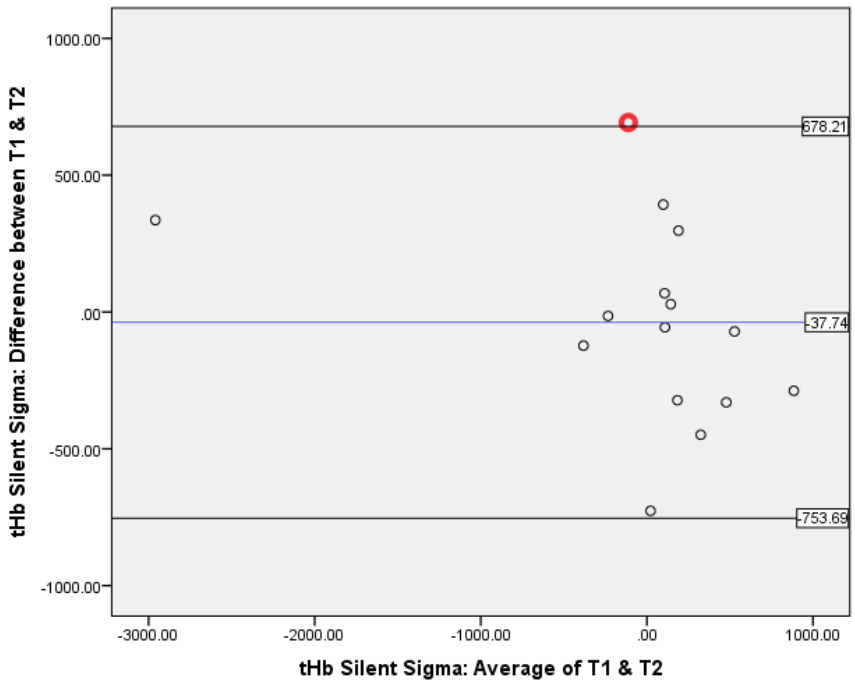


Figure 5d. Bland-Altman plot for tHb silent sigma values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .92.

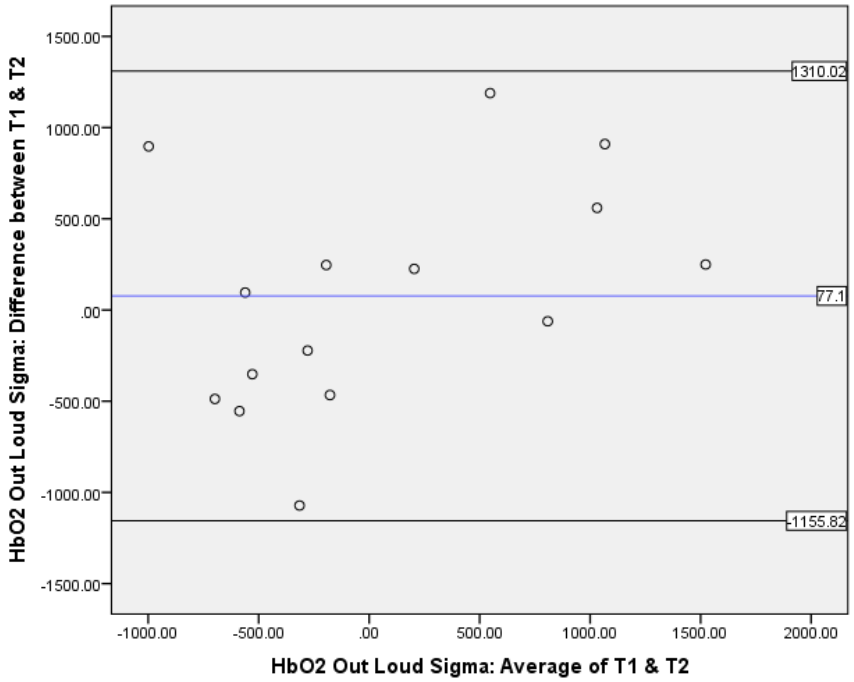


Figure 5e. Bland-Altman plot for HbO_2 out loud sigma values in TFC. There were no outliers. The ICC of the two trials was .71.

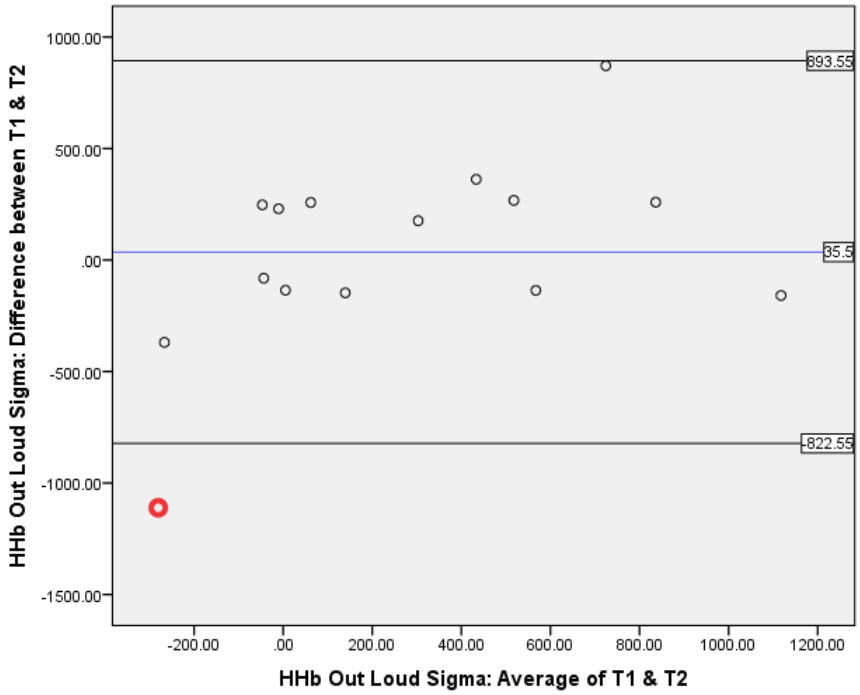


Figure 5f. Bland-Altman plot for HHb out loud sigma values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .57.

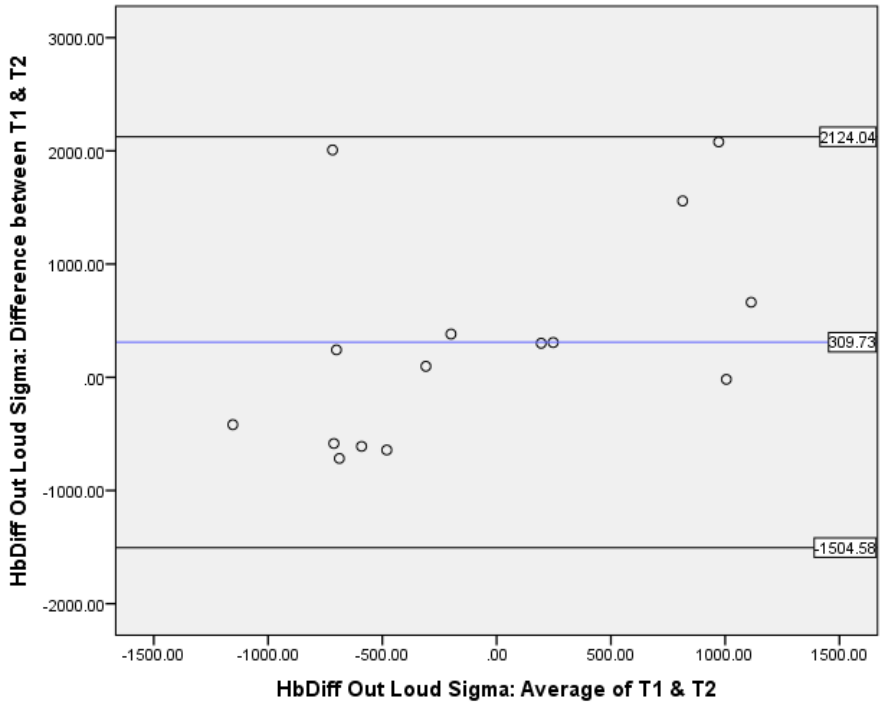


Figure 5g. Bland-Altman plot for HbDiff out loud sigma values in TFC. There were no outliers. The ICC of the two trials was .45.

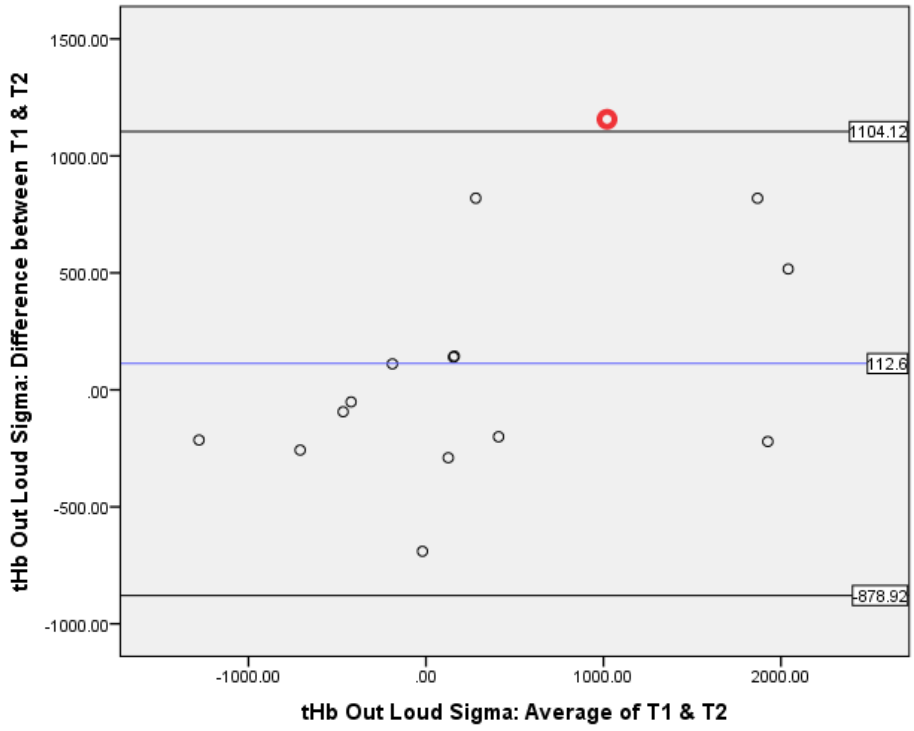


Figure 5h. Bland-Altman plot for tHb out loud sigma values in TFC. There was one outlier, which is indicated in bold red. The ICC of the two trials was .88.

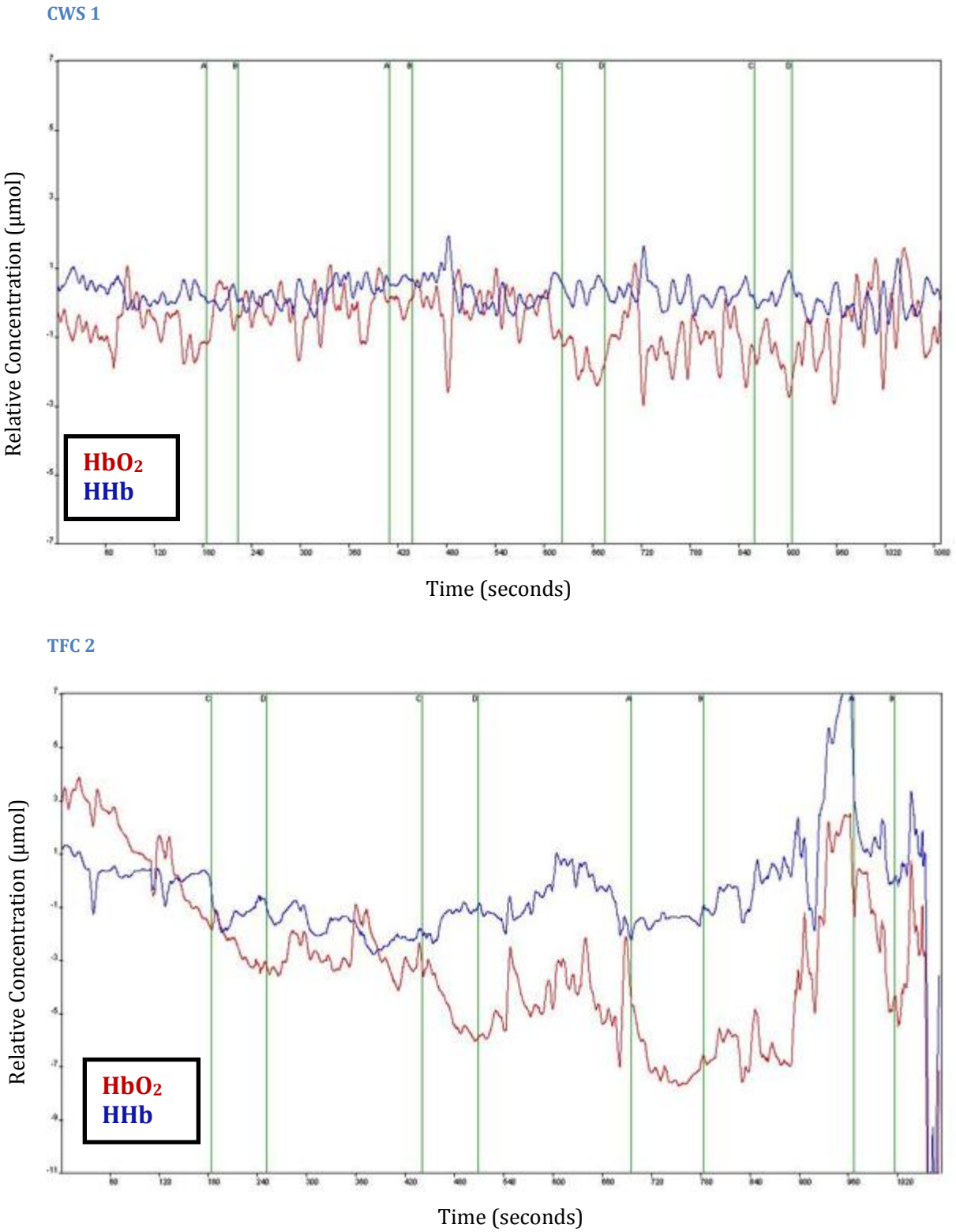
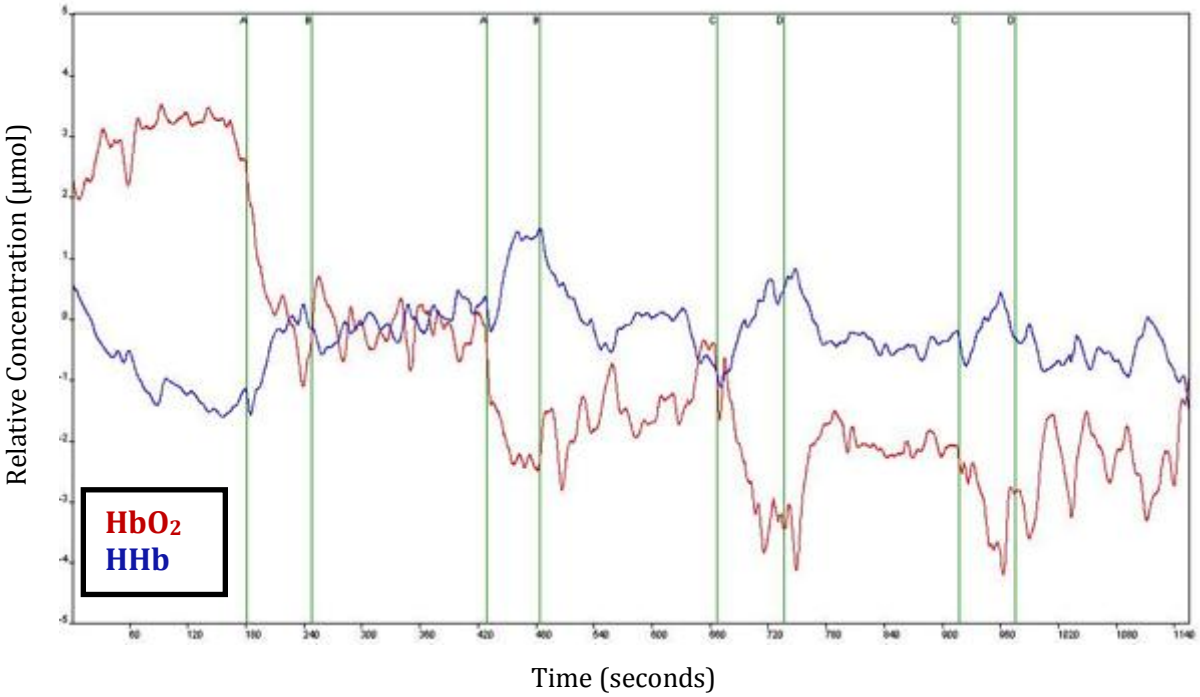


Figure 6a. fNIRS graphs for CWS-TFC Pair 1. Task periods are indicated as A-B sections (silent reading) and C-D sections (out loud reading).

CWS 2



TFC 4

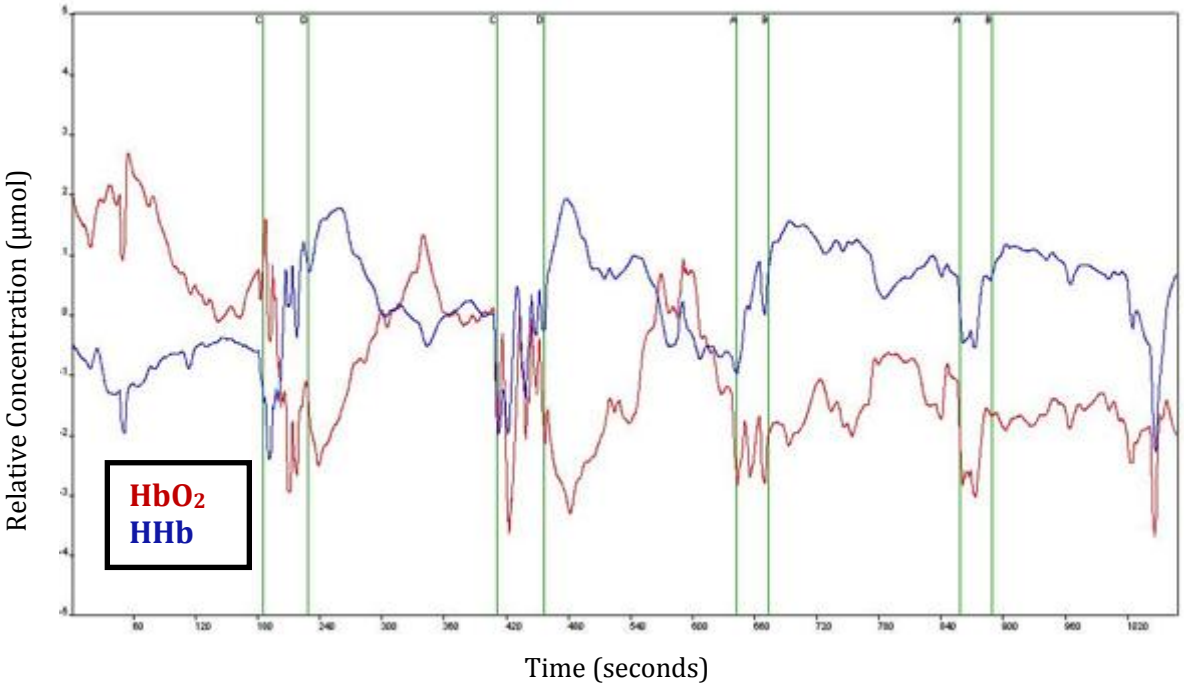


Figure 6b. fNIRS graphs for CWS-TFC Pair 2. Task periods are indicated as A-B sections (silent reading) and C-D sections (out loud reading).

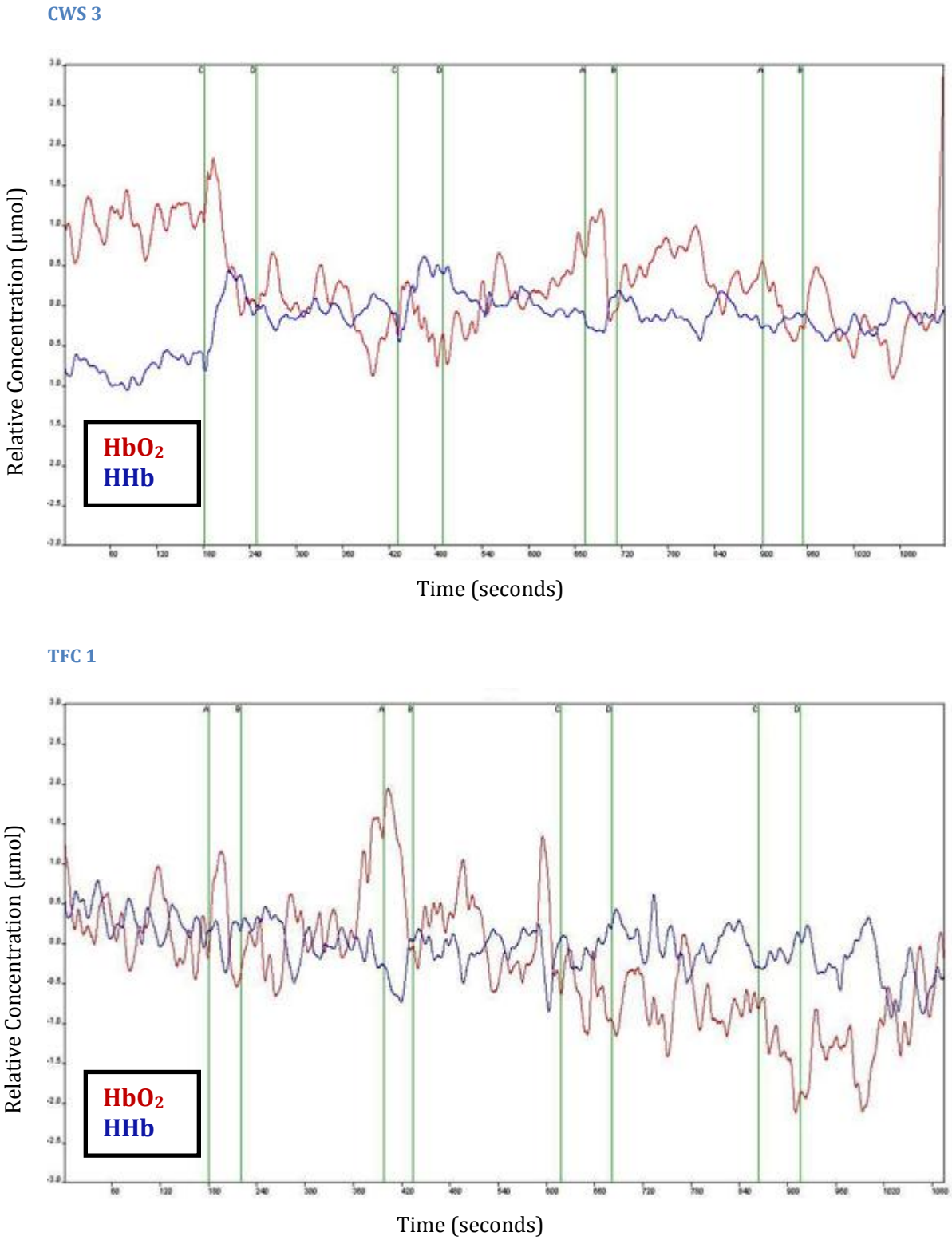
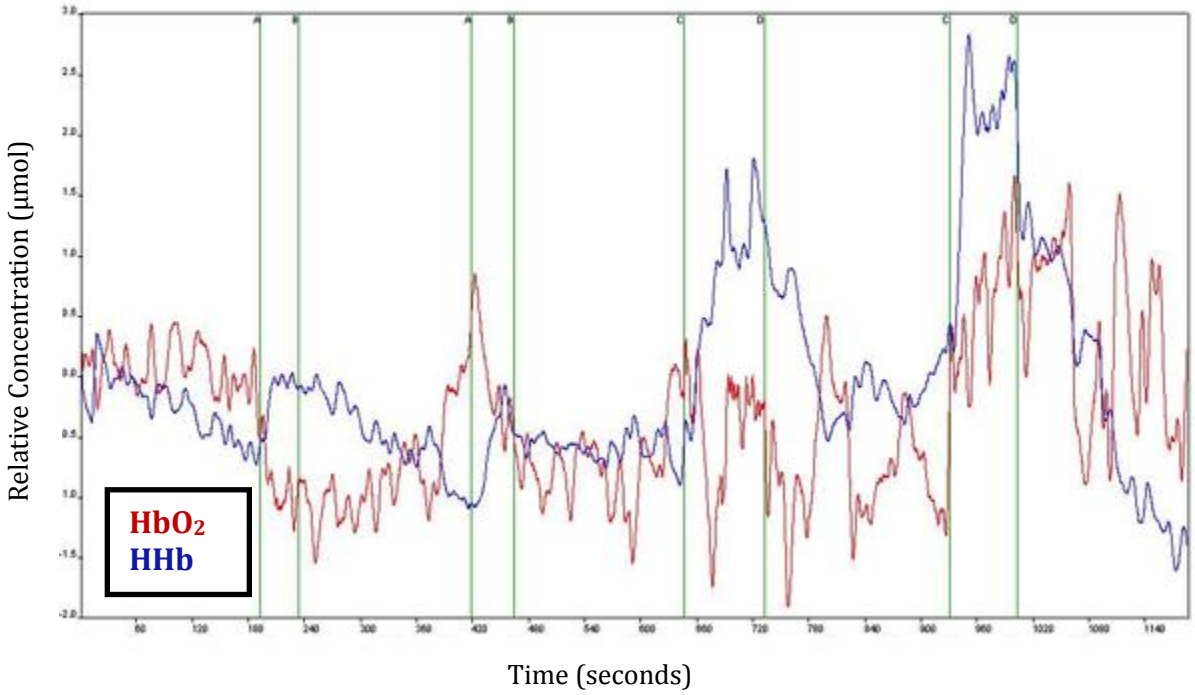


Figure 6c. fNIRS graphs for CWS-TFC Pair 3. Task periods are indicated as A-B sections (silent reading) and C-D sections (out loud reading).

CWS 4



TFC 12

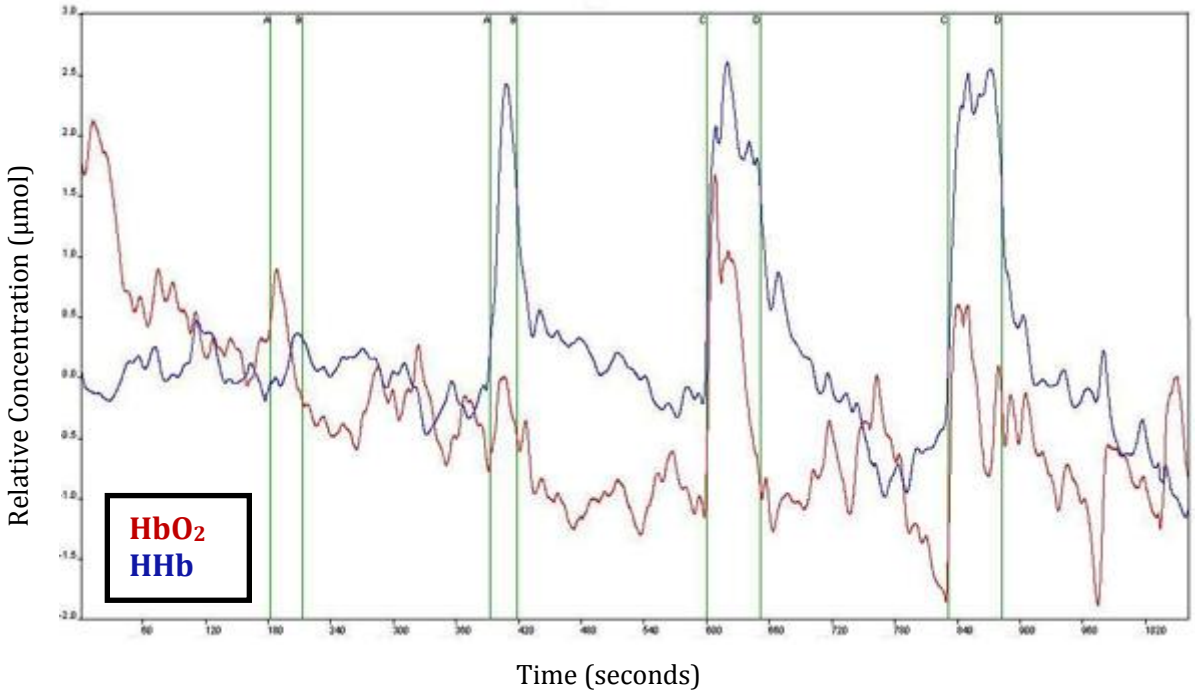


Figure 6d. fNIRS graphs for CWS-TFC Pair 4. Task periods are indicated as A-B sections (silent reading) and C-D sections (out loud reading).

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Appendix A: Recruitment Poster

Brain Activity in School-age Children who Do and Do Not Stutter

Would your child like to take part in a research study?

If your child is:

- Between 9 and 12 years old
- Right handed
- Boy or girl who does or does not stutter
- If your child stutters, he/she has not participated in an intensive therapy program in the last year

Study Requirements

- Two testing sessions of half an hour each
- Testing will be held at one of the testing sites in Edmonton or Calgary

If you are interested in this study, please contact:

Dr. Marilyn Langevin

Tel: 780 - 492 - 0975; E-mail: marilyn.langevin@ualberta.ca

Or

Catherene Joseph at cjoseph@ualberta.ca

Appendix B: Information Sheet for Parents

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

INFORMATION SHEET

Project Title: Relationship between Cerebral Oxygenation and Reading Fluency in Stuttering and Non-stuttering School-age Children: A Near Infrared Spectroscopy Pilot Study

Investigator(s):

Marilyn Langevin, PhD
Assistant Professor
Institute for Stuttering Treatment and Research, Faculty of Rehabilitation Medicine, University of Alberta
Tel: 780-492-0975
marilyn.langevin@ualberta.ca

Yagesh Bhambhani, Professor
Department of Occupational Therapy
Faculty of Rehabilitation Medicine
University of Alberta
Tel: 492-7248; E-mail:
yagesh.bhambhani@ualberta.ca

Luc De Nil, PhD
Department of Speech-Language Pathology
University of Toronto
Luc.Denil@utoronto.ca

Catherene Joseph, BA
Graduate Student
Faculty of Rehabilitation Medicine
University of Alberta
cjoseph@ualberta.ca

Background Information

Near infrared spectroscopy (NIRS) is a technique that uses light to measure brain activity. A small sensor is taped to the forehead. The sensor contains a light source and a detector. The sensor uses the light to detect oxygen levels in the blood within the brain. NIRS has been used to measure brain activity in children and adults. It has not yet been used to measure brain activity in people who stutter. In this study we will use NIRS to measure brain activity in children who do and do not stutter.

Purpose of the Study

This study asks three questions.
1. Does brain activity change when your child reads a paragraph twice?
2. Are there are differences in brain activity while reading between school-age children who do and do not stutter?

3. Are there differences in brain activity between reading out loud and reading silently?

What Your Child Will Do

Your child will need to come to two testing sessions. These can be scheduled on the same day. Your child will need to come to one of the following sites: (1) the Institute for Stuttering Treatment and Research (ISTAR) in Edmonton or Calgary, (2) your child's school, in a private, quiet room, (3) Dr. Bhambhani's laboratory at Corbett Hall at the University of Alberta in Edmonton, or (4) the University of Alberta office in Calgary. The testing sessions will take about half an hour each. The first testing session will consist of a speech, language and reading screening assessment. The second session will consist of NIRS testing procedures.

In the speech, language and reading screening assessments, your child will be assessed using typically used screening tests. The speech and language screening will be conducted by a qualified speech-language pathologist. The reading assessment will be conducted by a qualified reading specialist.

In the NIRS testing, we will first show you and your child the NIRS procedures. We will then ask your child to complete a handedness checklist to confirm that he/she is right-handed. In order to avoid your child being distracted during the NIRS testing session, you will be asked to wait outside the testing room. During the testing we will ask your child to read two short paragraphs. One paragraph will be read silently. The other paragraph will be read out loud. Each paragraph will be read twice. Between the readings, your child will be asked to sit quietly with his/her eyes closed for between 1-3 minutes. During these activities the NIRS equipment will measure your child's brain activity. This session will be videotaped for offline analysis of speech performance.

Before the first session, we will give you a consent form to complete. Your child will also be asked to complete a form to give their assent to participate in this study.

NIRS Measurements

To collect data, a sensor which has a light source and a detector will be placed on your child's left forehead just above his/her eyebrow. This sensor will be secured with an elastic bandage. The bandage does not contain any latex. To the best of our knowledge the fabric of the bandage is not made of allergenic materials. Although your child will be aware of the sensor placement, there are no specific discomforts associated with it. The sensor is shown in the picture on the next page. The equipment will be checked prior

to the session to make sure that it is working properly. Only a research assistant who knows how to use the equipment will test your child.

Risks

Your child will not feel anything unusual while the data are being collected. If you feel that your child cannot continue with the tasks for any reason, you can stop the session immediately. Your child can also stop the session immediately if he or she does not want to continue. We will also check in with your child at the end of each reading tasks to make sure he/she still wishes to participate. The technology that we will be using in this research has often been used with healthy children and adults as well as those who have a variety of disabilities. So far, no side effects have been reported.

Benefits

This research will provide important information on how NIRS can be used in stuttering research. It will provide information about differences in brain activity between school-age children who do and do not stutter. This will help us to understand why some children stutter using a cheaper and non-invasive tool. You will also be given the results of the speech, language and reading screening tests.

Confidentiality

All the personal information and test results will be kept confidential except when professional codes of ethics and/or legislation require reporting. Only the investigators listed on this information sheet and their research assistants will have access to your child's data. Any report published as a result of this study will not identify your child by name. The data will be kept for at least seven years after the study is completed. During testing, your child will be assigned a code which will be known only to the investigators and the research assistants. Your child's electronic data files, including video data, will be stored on a password secured computer. Printed copies of the data will be locked in a filing cabinet in the principal investigator's office.

Freedom to Withdraw

Participation in this study is voluntary. You are free to withdraw your child from the study at any time. If your child is a person who stutters, your decision to withdraw from the study will not affect your or your child's relationship with the Institute for Stuttering Treatment and Research or any speech-language pathologist that is working with your child. Your child will continue to receive the same treatment if you choose to have him/her drop out of the study.

If any knowledge gained from this or any other study becomes available which could influence your decision to have your child continue in this study, we will inform you promptly.

Reimbursement of Expenses

If you live outside of Edmonton and travel to Edmonton to participate in the study, you will be reimbursed $100 for one night's accommodation. If you live outside of Calgary and travel to Calgary to participate in the study, you will be reimbursed $100 for one night's accommodation. You will also receive $50.00 for food and transportation. All participants will receive a gift certificate valued at $15.00 for the time spent in this project. Your child will choose the gift certificate that he or she wants from a number of choices.

Contact

If you have any questions about this study, please contact Dr. Marilyn Langevin at 780-492-0975, Dr. Bhambhani at 780-492-7248 or Catherene Joseph. Catherene Joseph can be reached by phoning 780-492-2619 and leaving a message for her, or by contacting her at cjoseph@ualberta.ca. She will also be scheduling the testing sessions.

If you have concerns about your rights or any part of this study, you can contact Charmaine Kabatoff with the Health Research Ethics Board. She can be reached at (780) 492-0302. This office has no affiliation with the investigators.

This picture shows the sensor with the light source and detector of brain activity.

Appendix C: Child Information Sheet and Assent Form

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

CHILD INFORMATION SHEET AND ASSENT FORM

Title of Research Study:	**Brain Activity in School-age Children who do and do not stutter**
Principal Investigator:	**Marilyn Langevin, PhD.** Phone: (780) 492-0975; marilyn.langevin@ualberta.ca
Co-Investigators:	**Catherene Joseph, B.A.** Email: cjoseph@ualberta.ca **Yagesh Bhambhani, Professor** Phone: (780) 492-7248 **Luc De Nil, Professor and Chair** Email: Luc.Denil@utoronto.ca

This study will help us learn about brain activity in kids who don't stutter and kids who do stutter. Stuttering makes it hard to speak for lots of kids all over the world.

What will you do?

If you take part in this study, you will need to come to two testing sessions. Each session will take about a half an hour. When you come, we will ask you to sign a form. This tells us you want to be in the study. In the first session, we will ask you to do a few word and reading exercises. This helps us to learn about the way you read. In the second session, we will show you how we measure brain activity. Then we will show you how we measure brain activity. You can see the equipment in the picture on the next page. After you have the equipment on, we will ask you to read. You will read two short paragraphs. You will read one paragraph silently and one out loud. You will read each paragraph twice. Between the readings you will rest with your eyes closed for a few minutes. You can ask us questions if you are not sure about anything or want to know more about something. We will do a short practice round before we start so you can get comfortable.

Will you get anything out of it?

By being in this study, you will help us to learn more about more about what the brain does when kids are reading. You will learn how brain activity can be measured. You will also be able to choose a $15.00 gift card as a thank you for your time.

Can you quit?

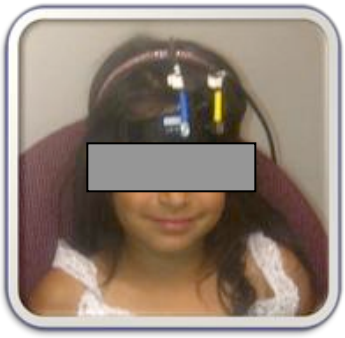
You don't have to be in this study if you don't want to. You can stop at any time, and that is okay. You just need to tell us that you want to stop and we will do that. At the end of each reading, we will ask you if you want to continue. If you do not want to continue, we will stop.

Will your name be used in the study?

We will not use your name in anything that we write about the study. Only the research team will know who participates in the study. The names of the people on the research team are at the top of the first page. Sometimes, there may be research assistants who help us.

Do you have more questions?

If you have more questions, you can talk to Dr. Marilyn Langevin who is leading the study. Her phone number is (780) 492-0975. You can email her at marilyn.langevin@ualberta.ca. If you want to talk to her, ask your parents to help you contact her.



<u>Your signature</u>:

If you want to be in the study you will need to sign your name below. Your mom or dad also needs to sign a form that says that they will let you be in the study.

I agree to be in the study.

_____	_____
Your signature	Date
_____	_____
Signature of witness	Date
_____	_____
Signature of investigator	Date

Appendix D: Parent Consent Form

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

CONSENT FORM

Part 1 (to be completed by the Principal Investigator):

Title: **Relationship between Cerebral Oxygenation and Reading Fluency in Stuttering and Non-stuttering School-age Children: A Near Infrared Spectroscopy Pilot Study**

Principal Investigator(s): Marilyn Langevin, PhD
Co-investigator(s): Yagesh Bhambhani, PhD; Luc De Nil, PhD; Catherene Joseph, BA

Part 2 (to be completed by the parent/legal guardian of research subjects):

Do you understand that your child has been asked to be in a research study? Yes No

Have you read and received a copy of the attached Information Sheet? Yes No

Do you understand the benefits and risks involved with your child taking part in the speech and language screening, reading assessment, and NIRS testing which will be videotaped? Yes No

Have you had an opportunity to ask questions and discuss this study? Yes No

Do you understand that you are free to withdraw your child from the study at any time without giving a reason, and without your decision affecting your child's speech therapy, if he or she is receiving any? Yes No

Has the issue of confidentiality been explained to you? Do you understand who will have access to your child's records? Yes No

Do you want the investigator(s) to inform your child's family doctor that he/she is participating in this research study? Yes No

If so, please provide your doctor's name: _____

This study was explained to me by: _____

I agree to have my child take part in this study.

_____ _____ _____
Signature of Parent/Guardian Printed Name Date

_____ _____ _____
Signature of Parent/Guardian Printed Name Date

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to have their child participate.

_____ _____
Signature of Investigator or Designee Date

Appendix E: Letter to Teachers

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

(Date)

Dear teachers,

Re: Investigating brain activity in children who do and do not stutter

We are conducting a study that aims to investigate brain activity during reading in school-age children who do and do not stutter. This study has been approved by both the University of Alberta and the Edmonton Catholic School Board. The results of this study have the potential to help us better understand stuttering, what goes on in the brain during reading in children who do not stutter in comparison to children who stutter, and also to help children who stutter.

We are inviting children in your classes to participate in this study as a part of the 'children who do not stutter' group. The study will be comprised of two testing sessions, for which students will need to be taken out of the classroom. The first will be the administration of the Woodcock Reading Mastery Test III by a qualified speech-language pathologist. This session will take anywhere from 15-45 minutes, depending on the child. The results of this assessment will be made available to you and your school, so that you can compare them to reading assessments that have been conducted by the school. The second session will be the brain-imaging session, in which children will be asked to read two short paragraphs while their brain-activity is measured using near-infrared spectroscopy, a form of non-invasive brain imaging technology. This session will take approximately half an hour.

We greatly appreciate your cooperation and help in conducting this study. Should you have any questions or concerns, please contact Dr. Marilyn Langevin at 780-492-0975 or marilyn.langevin@ualberta.ca. You may alternatively contact Catherene Joseph at 780-729-7624 or cjoseph@ualberta.ca.

Yours sincerely,

Marilyn Langevin, PhD, R.SLP, S-LP(C), CCC-SLP

Assistant Professor

Director of Research

Appendix F: Letter to Parents

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

Re: Investigating brain activity in children who do and do not stutter

Dear Sir/Madam

We are conducting a study that aims to investigate brain activity during reading in school-age children who do and do not stutter.

Purpose of the Study

This study asks three questions.
1. Does brain activity change when your child reads a paragraph twice?
2. Are there are differences in brain activity while reading between school-age children who do and do not stutter?
3. Are there differences in brain activity between reading out loud and reading silently?

Both the University of Alberta and the Edmonton Catholic School Board have approved this study. The results of this study have the potential to help us better understand stuttering, what goes on in the brain during reading in children who do not stutter compared to children who stutter, and also help children who stutter.

Eligibility Criteria

Your child is being invited to participate in this study as part of the 'children who do not stutter' group. In order to be eligible to be a part of this group, your child must:

- be right-handed
- have no history of reading difficulties or neurological deficits, including a diagnosis of acquired neurogenic stuttering, hearing, language or other speech disorders.

Study Requirements

If your child chooses to be a part of this study, he/she will take part in two research sessions. The first will be a reading assessment conducted by a qualified speech-language pathologist. The result of this assessment will be made available to you. They will also be made available to the school, which can then compare them to the school-conducted reading assessments so as to give you a more comprehensive evaluation of your child's reading skills. The second research session will be the brain imaging session, where your child will be asked to read two passages while their brain activity is monitored with non-invasive brain-imaging technology. This technology is near-infrared spectroscopy, and it is described in the attached information sheet. Although your child will be aware of the sensor placement, there are no specific discomforts associated with it. This session will be videotaped in order to ensure adherence to study protocol and to allow for offline analysis of speech-performance by our speech-language pathologists.

How you and your child will benefit from this study

Both you and the school will receive the results of the reading test, as well as a summary of our study findings related to the three research questions above. In addition to this information, your child will also be given a gift certificate valued at $15.00 as a thank-you for the time spent in this project. Your child will be able to choose the gift certificate that he or she wants from a number of choices.

Please find attached information sheets for you and your child to review. These information sheets will give you a more detailed description of the study. Your participation is greatly valued and appreciated. Please note that we are looking for a small number of participants, and slots will be filled on a first-come-first-served basis. If you are interested in having your child take part in this study, please contact [*insert name of contact*] at your earliest convenience.

If you would like more information about this project, please contact Dr. Marilyn Langevin at 780-492-0975 or marilyn.langevin@ualberta.ca.

Thank-you for taking the time to review this invitation.

Yours sincerely,

Marilyn Langevin, PhD, R.SLP, S-LP(C), CCC-SLP

Assistant Professor

Director of Research

Appendix G: Address Form

Institute for Stuttering Treatment and Research (ISTAR)

Communication Improvement Program (CIP)

If you are interested in receiving a summary of the findings of this study in the mail, please circle 'Yes' and provide your address below. Thank-you.

I would like to receive a summary of this study's findings. **YES / NO**

Name: _____

Mailing Address: _____

_____

_____

Appendix H: fNIRS Children Recruitment, Preparation, Familiarization and Testing Protocol

fNIRS Children Recruitment, Preparation, Familiarization and Testing Protocol

A. Recruitment Procedures

B. Screening Tests

C. Equipment Preparation

D. fNIRS Familiarization and Practice

E. fNIRS Testing

F. Data Management

G. Data Analysis

A. Recruitment Procedures

1. Recruitment methods: poster, through schools, past clients, Alberta Health Services
2. Send recruitment package to PWS and Controls (information sheet, consent/assent forms)
3. When potential participants contact us, review inclusion criteria and study details with them, as needed

Eligibility: you are

- 9-12 years of age
- Right handed
- Male or female who does or does not stutter
- Have no history of neurological problems including a diagnosis of stuttering acquired from a stroke, hearing, language, or other speech disorders
- If you are a person who stutters, you have not participated in an intensive therapy program in the previous year

4. Schedule testing
6. Enter participant information (name/contact information) into participant database

B. Screening Tests

1. Review the information sheet with parent and child and obtain informed consent from parents and assent from child
2. Collect demographics: name, gender, age, time of testing, treatment history (if any)
3. Complete Edinburgh Handedness Inventory with child
4. Complete reading screening
5. Complete CELF-IV screening and Oral Mechanism Exam
6. Determine eligibility:
    (a) if eligible invite to fNIRS testing
    (b) if not eligible, thank and give $15 iTunes gift certificate

C. Equipment Preparation

1. fNIRS system set up
2. Video-recorder and mic set up and ready
3. Glass of water
4. Reading passages organized
5. Podium on table

D. fNIRS Familiarization and Practice

1. Briefly explain the fNIRS equipment and the study purpose.

2. "These sensors will be measuring your brain activity." [Strap sensors in place and ensure participant is comfortable and that nothing is in their way]

2. Review procedure:
    a) We are going to be measuring your brain activity while you read.

    b) First you are going to close your eyes and rest for a few minutes. When you open your eyes, you will see a paragraph in front of you. You will read that paragraph [out loud/silently]. After you read this, you will get to rest with your eyes closed for a few minutes again. Then we will repeat the same thing over again. After that, we will give you another paragraph to read. You will read this paragraph [out loud/ silently]. After you finish reading, you will close your eyes and rest again. Then you will repeat the same thing over again. I will tap you on the shoulder each time it is time for you to start reading again.

c) The resting time might seem long, but it is not. Remember to close your eyes every time you finish reading so that I know you are finished.

d) If you want to stop at any time, you can let me know and it's ok.

3. "Let's practice. We will only use a short rest period and short readings for this practice."

Baseline: "Okay, sit quietly and close your eyes." (time for 15 seconds)
Silent Reading: [Place practice passage in front of subject – TITLED READ SILENTLY]
Baseline:
Second silent reading:
Baseline:
First oral reading:
Baseline:
Second oral reading:
Baseline:

4. RANDOMIZED ORDER OF PASSAGE PRESENTATION: explain "Whether you are given the oral reading task or the silent reading task first will be randomly determined by having you select a number between 1 and 100." [CODE: Odd= Silent first; Even= Out loud first]

5. "Do you have any questions? Are you comfortable and can you easily read from the sheet [ensure that the participant can read; adjust the height of the table/podium as needed]. We want you to be able to open your eyes and begin reading without have to adjust your body or head position."

6. Once participant is seated comfortably and ready to begin, clip mic to their shirt.

7. "Before we begin, you can have a little drink if you like – I have poured water for you."

8. "The last thing before we begin – I need your age to set the computer system."

E. fNIRS Testing

1. Turn on video camera and mic
2. Press recording button on computer to start fNIRS recording
3. Begin with 3 minutes of rest
4. Place passage [either silent or out loud, depending on random order] in front of participant and at the 3 minute mark, tap them on the shoulder to indicate that it is time for them to start reading. [mark events on the trace (i.e., reading begins/ends) as they occur by pressing F4]
5. Once they have closed their eyes indicating that they have finished reading the first passage, begin the next timed rest period. After the 3 minutes have passed, the participant will re-read the first passage.
6. Rest period of 3 minutes after which the participant will read the second passage. Once they have finished, they will rest for another 3 minutes before re-reading the second passage.
7. Finish with 3 minutes of rest.
8. Press stop button on computer to stop fNIRS recording; turn off video camera and mic.
9. Thank participant for their time and give them a $15 iTunes gift certificate.

F. Data Management

1. Save data file according to participant type and number (i.e., CWS_01 (child who stutters #1)/ TFC_01 (typically fluent child #1))

2. Data files are to be stored in the NIRS ISTAR folder on the desktop in the sub-folder 'Children's Study'

Appendix I: Silent Reading Passage (Grandma is Coming)

Grandma is coming for a visit. She is coming in her big car. Timothy made a picture for her. Anna is going to show her a dance. They are hoping she will arrive soon. They want to go to the park. Grandma will push Timothy and Anna in the swing. When they go down the slide, Grandma will take their picture. On the way home, they will get an ice cream cone. Grandma plays the piano. Timothy and Anna like to sing. They like it when she plays "Big Rock Candy Mountain." When Grandma comes, they will play and sing. Then Grandma will read each of them a story. Timothy has a new book that he wants her to read.

Anna and Timothy are waiting for Grandma by the window. "Is she here yet?" they ask.

Appendix J: Out Loud Reading Passage (Nicknames)

The word nickname means “added name.” Nicknames are used in place of a person’s real name. Some nicknames are based on a person’s first name. For example, Matt is a nickname for Matthew. Some nicknames are based on what a person has done. John Chapman traveled around the country handing out apple seeds. Now he is known as Johnny Appleseed.

Nicknames can also be based on how a person looks. A person with red hair might be called Red or Carrot-top. A lot of people in politics have nicknames. Some are nice nicknames. Some are not very kind. Some people are given nicknames based on where they were born. Moms and dads often use nicknames, like Honey or Dear, when they talk to each other, too. Do you have a nickname?

Appendix K: Silent Reading Practice Passage

For more than 200 years we have used toothbrushes similar to the one the prisoner invented. Toothbrushes are not made out of bones anymore. They come in all kinds of colors, shapes, and sizes. The next time you brush your teeth, think about the prisoner in England who invented the toothbrush.

Appendix L: Out Loud Reading Practice Passage

Did you know that the toothbrush was invented in a prison? One morning in 1770, a man in an English jail woke up with a new idea. He thought it would be better if he could use a brush to clean his teeth, rather than wipe them with a rag.