Investigating Speech Motor Control Using Vocal Tract Imaging, fMRI, and Brain Stimulation

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Abstract

The aim of this thesis was to understand speech motor control in both people who are typically fluent (PWTF) and people who stutter (PWS). To do this, I used a multi-modal approach including vocal tract MRI, functional MRI during task and brain stimulation. These methods allowed me to explore speech motor control from the brain's control of speech to the movement of the articulators.

First, I conducted a systematic review of previous studies of articulation in PWS that used a variety of different methods. Technological advances over the last 15 years have offered new insight into the speech motor control of PWS by measuring precise movements of the articulators involved in speech.

I then used vocal tract MRI (vtMRI) to look at the speech movements in PWS. As this is a novel technique, experiments have been designed to first replicate and then extend key results identified via the systematic review that used alternative methods. We found that PWS, on average, produced more variable movements than typically fluent speakers even during fluent productions of simple nonwords. This indicates general, trait-level differences in the control of the articulators between PWS and people who are typically fluent.

I used functional MRI of the brain to investigate differences in the neural control of speech in PWS and PWTF. I used a task known as the Stop-Signal task that was previously used to investigate inhibitory motor control in both speech and manual movements (Xue, Aron &

Poldrack, 2008). The results support the role of an over-active inhibitory response in PWS compared with controls.

Finally, I designed a study to investigate whether transcranial direct current stimulation (tDCS) can modulate speech articulation in a typically fluent population. I used both behavioural and electrophysiological outcomes to assess the role of tDCS in modulating performance on a complex articulation task. TDCS did not modulate performance on a complex articulation task in healthy young adults. TDCS applied concurrently with task learning also failed to modulate cortical excitability in expected ways.

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1 Introduction

The human ability to produce rapid, fluent speech is astonishing. The ease with which many communicate hides the complexity of the function being carried out. In just one second of speech we can produce approximately ten speech sounds that require the precise co-ordination of over 100 muscles. However, producing effortless, fluent speech is not always easy. For example, the speech of people who stutter is characterised by frequent interruptions to its flow. These interruptions include repetitions and prolongations of speech sounds, as well as temporary failure to initiate a speech sound, known as a 'block'. Contrary to earlier interpretations of stuttering as a consequence of anxiety, the contemporary view of developmental stuttering is of a speech motor disorder with a distinct neural profile.

Understanding speech motor control in both people who are typically fluent and those who stutter is the overarching goal of this multimodal thesis.

1.1 Speech Motor Control

Speech production is a procedural skill that requires three steps: conceptualisation, formulation, and articulation. Levelt proposed a model of word production that captures the process of speech from thought, or concept, selecting the correct lexical units (or *lemmas*) and then encoding the form of these *lemmas* in terms of morphemes and phonemes, with prosodification and syllabification to assemble the phonetic code for production (Levelt, 1989). To produce the planned utterance, the phonetic code needs to be articulated using the

vocal tract. Typically, speech is produced via pulmonary pressure from the lungs that generate sound by phonation through the glottis in the larynx. This air pressure is then passed into the vocal tract, the shape of which is modified by articulators such as the velum, tongue and lips that move rapidly to produce vowels and consonants. An image of the vocal tract is shown in Figure 1.1.

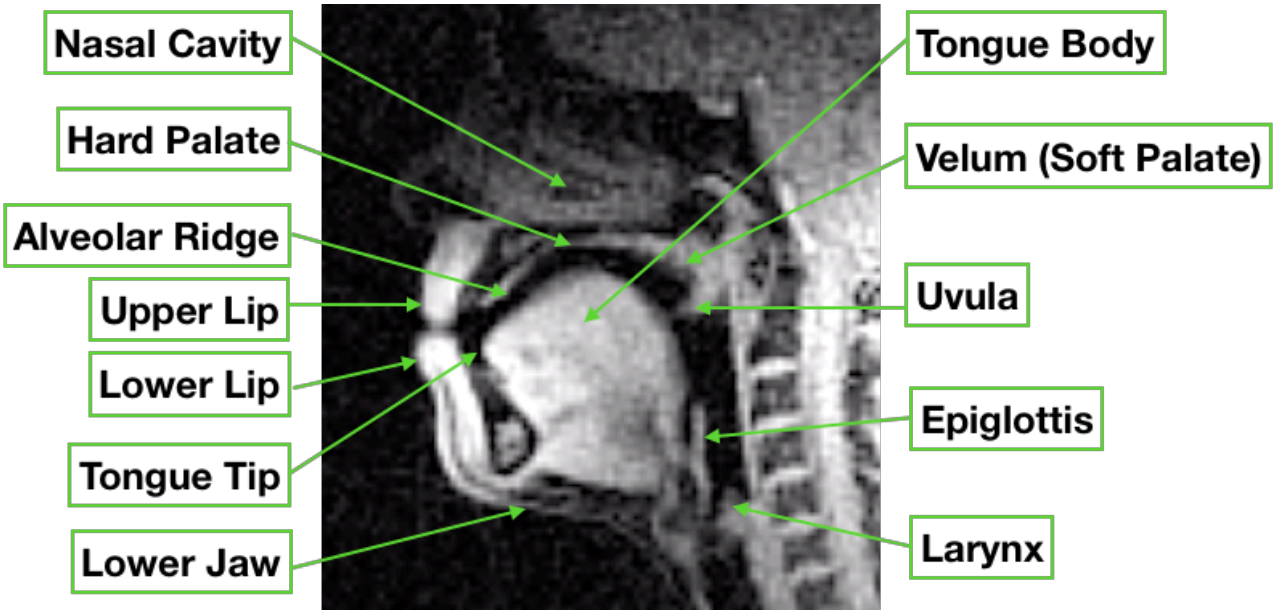


Figure 1.1 Anatomy of the Vocal Tract.

A single frame from a vocal tract MRI session (during the M in 'mab'). Tissue in white, air and bone in black. Teeth are not shown using this contrast.

1.2 The brain and speech motor control

Modern neuroimaging techniques have enabled researchers to identify areas of the brain that contribute to speech production. The continuous integration of auditory, somatosensory and

motor information during speech production requires tightly controlled and co-ordinated action of a large number of cortical and subcortical regions.

The DIVA (Directions Into Velocities of Articulators) model provides a neural network account of the phonological encoding and articulation stages of Levelt's model (Guenther, 2016). According to this theory, speech production starts with activation of the sound's neural representation in a *speech sound map* thought to reside in the left ventral premotor cortex (Kearney & Guenther, 2019). This then projects to motor maps representing the articulators in primary motor cortex. Subcortical regions including the putamen, caudate nucleus, and thalamus are responsible for the initiation of a speech sound, in turn projecting to the supplementary motor area (SMA) and motor cortex. The speech output is then constantly monitored using feedforward and feedback mechanisms. Feedforward information is the stored instructions of how the articulators should move to produce a certain sound. Feedback loops are slow and involve monitoring of the somatosensory and auditory output (sensory reafference).

Auditory feedback is used to compare auditory targets (or predictions) with auditory state maps. If the action deviates from the plan too much (e.g. an unexpected formant pattern is heard), an error signal is produced resulting in activation of the posterior auditory cortex. Corrective motor commands are then activated through projections from the auditory error nodes to the right ventral premotor cortex, which in turn projects to the articulator map in the ventral motor cortex. Somatosensory feedback is processed in a similar fashion but relies on proprioceptive information of the current state of the articulators (e.g. monitoring of the tongue position) (Kearney & Guenther, 2019).

This model provides testable hypotheses as to the involvement of each stage of the model and the associated neural underpinnings. Damage to each of these stages is hypothesized to result in speech and language disorders including dysarthria, stuttering and cluttering. For example, developmental stuttering may result from an impairment of the fast feedforward control or an over-reliance on the slow sensory feedback mechanisms or both (Civier, Tasko, & Guenther, 2010; Guenther, 2016; Van Lieshout, Hulstijn, & Peters, 2004, 1996b). Such abnormalities would lead to an accumulation of error signal that in turn leads to corrective movements, such as the pauses and repetitions characteristic of stuttering (Civier et al., 2010).

1.3 Developmental Stuttering

Developmental stuttering is characterised by frequent interruptions to the flow of speech. These interruptions include repetitions and prolongations of speech sounds, as well as temporary failures to initiate a speech sound, known as 'blocks' (See Figure 1.2, below). Developmental stuttering is first identified in early childhood and affects 5% of children (Andrews & Harris, 1964). Spontaneous recovery is common, resulting in 1% of the adult population continuing to stutter (Yairi & Ambrose, 2013). There is a gender bias in both the emergence and recovery of stuttering; four times as many males continue to stutter into adulthood (persistent stuttering) than females (Yaruss & Quesal, 2004). Contrary to earlier interpretations of stuttering as a consequence of anxiety, the contemporary view of developmental stuttering is that it is a speech motor disorder with a distinct neural profile.

1.3.1 Primary Characteristics

People who stutter vary greatly in the amount to which they experience disfluent moments, including blocks, repetitions and prolongations. It is worth noting that the majority of the speech of a person who stutters is fluent and disfluencies occur for between 5 and 20 percent of syllables spoken by a person with a moderate stammer. When stuttered moments do occur, they can vary in their intensity, in terms of the duration and amount of tension involved. An example of these primary characteristics during naturalistic speech is shown in Figure 1.2.

However, there is a pattern to the placement of stuttered moments within speech: in general, stuttered moments are far more likely to occur at the beginning of a word or sentence (Howell & Au-Yeung, 2002) and rarely, if ever at the end. This suggests that stuttering reflects failures in the planning and initiation of speech sounds.

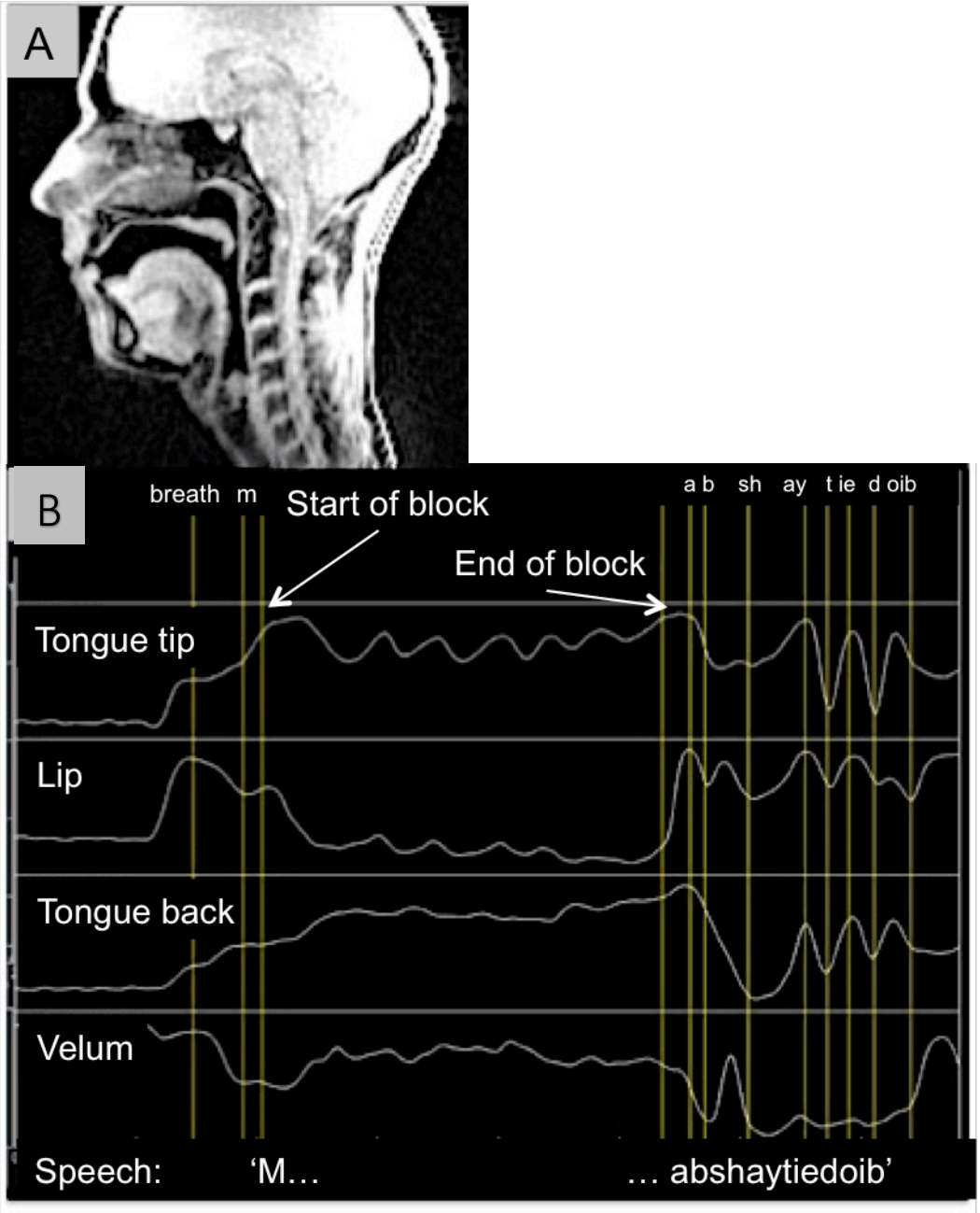


Figure 1.2 Example of a block.

A) A single frame demonstrating muscle tension during a block. The lip is curled around the teeth (note that teeth are not visible using this method), tongue is held down, velum raised. B) Tracking of the articulators during the block. Yellow lines correspond to key articulator movement, with a label above each one.

1.3.2 Secondary Characteristics

Secondary characteristics often occur as a consequence of stuttering. They can be voluntary or involuntary. Voluntary body movements include rhythmic tapping of the hands or feet, swaying of the body or head movement. These can provide rhythmic support, which is thought to help with the initiation of speech sounds (see below). Involuntary movements, on the other hand, take the form of increased tension primarily in the muscles of the face or neck during a disfluent moment. These can range from subtle to strong, uncomfortable movements that have been likened to tics that occur in disorders such as Tourette's syndrome. Finally, people who stutter may produce more non-speech movements, resulting in sounds such as 'umm' or 'err'. These non-speech sounds are common in everybody's speech. They may be used to give more time to plan the speech to be produced, for either cognitive or phonetic reasons. People who stutter may rely on such tactics to a greater extent.

Both primary and secondary characteristics are important in the maintenance of stuttering. It is important therefore that both are captured in our attempts to measure the severity of stuttering in an individual. The Stuttering Severity Instrument (SSI; Riley, 2009) is used to measure the presence and severity of both primary and secondary characteristics. This instrument was used throughout this thesis to measure the severity of developmental stuttering in the participants studied.

1.3.3 Psycho-Social Characteristics

A combination of genetic, neurobiological, and developmental factors has only recently been considered the cause of developmental stuttering. For a long time, developmental stuttering

was thought to occur as a result of anxiety or trauma or both. The prevailing idea that anxiety caused stuttering was held because PWS are more likely to be anxious compared to people who are typically fluent (PWTF) (Blood et al., 2011; Bricker-Katz, Lincoln, & McCabe, 2009; Iverach & Rapee, 2014). However, it is known that anxiety is a common consequence of living with a stutter, and does not cause DS (Craig & Hancock, 1996).

1.4 Neural differences in PWS

Brain imaging studies reveal a number of regions of the brain that are different in PWS compared with PWTF (Belyk, Kraft, & Brown, 2015; Brown, Ingham, Ingham, Laird, & Fox, 2005; Budde, Barron, & Fox, 2014; Neef, Anwander, & Friederici, 2015; Watkins, Smith, Davis, & Howell, 2008). Many of these areas contribute to a cortico-basal ganglia-thalamocortical motor loop that controls speech (Alm, 2004; Bohland, Bullock, & Guenther, 2010). However, the role of each of these brain regions and their relation to stuttering remains unclear. The complex interconnection between areas in this network means that the causal difference could be in subcortical areas themselves, cortical areas, or in the connections between areas.

Below, I briefly review evidence relating to different explanations for the neural differences in people who stutter and potential causes of stuttering.

1.4.1 Hemispheric Lateralisation

In the typically speaking, right-handed population, speech is very likely to be lateralised to the left. That is, left hemisphere regions including prefrontal, temporal and motor regions

dominate the control of speech. A large body of research has revealed that PWS show underactivation in the left hemisphere speech network and hyperactivity in right hemisphere homologues during speaking compared with PWTF (Belyk et al., 2015; Braun et al., 1997; Brown et al., 2005; De Nil, Kroll, Kapur, & Houle, 2000; Kell et al., 2009; Neef et al., 2015; Watkins et al., 2008). For example, work using PET to measure regional cerebral blood flow found right-greater-than-left asymmetry of motor and auditory regions during stuttered speech, which normalised when fluency was induced using choral reading (Fox et al., 1996). In support, speech therapy resulted in near-normalisation of the overactivity in the right hemisphere (De Nil, Kroll, Lafaille, & Houle, 2003; Kell et al., 2009) and underactivity in the left hemisphere (Kell, Neumann, Behrens, von Gudenberg, & Giraud, 2018; Neumann et al., 2018).

Recent evidence attempted to understand the function of the left and right hemispheres by recording fMRI during fluent and dysfluent speech. Right hemisphere hyperactivation was associated with state level stuttering: during dysfluent states relative to fluent, there was greater activation of inferior frontal and premotor cortex extending into the frontal operculum, bilaterally. In contrast, reduced activation of left auditory cortex, inferior frontal cortex and medial cerebellum were general traits that distinguished fluent speech in people who stutter from that of controls (Connally et al., 2018).

Lateralisation differences are also seen in white matter connectivity using diffusion MRI. Specifically, studies found reduced integrity of the white matter underlying the left sensorimotor cortex (Connally, Ward, Howell, & Watkins, 2014; Watkins et al., 2008) and

greater mean diffusivity in the frontal aslant tract (FAT) connecting the IFG with the SMA/pre-SMA (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016). This reduction in connective strength could hinder the precise control of the fine motor movements involved in planning and producing speech, which could contribute to stuttering. In contrast, greater structural connectivity between the right IFG and SMA and right IFG and thalamus was found in PWS compared to PWTF (Neef, Anwander, et al., 2018). This suggests stronger learned use of this network in PWS compared with controls (Neef, Anwander, et al., 2018; Neef et al., 2015; Xue, Aron, & Poldrack, 2008).

The neuroimaging results described so far paint a picture of underactivity and reduced connectivity in the left hemisphere regions in the speech network and overactivity and increased connectivity in the right hemisphere homologues in PWS compared with PWTF. However, it is not clear what the precise nature of this activation is. In addition, it is not well understood which differences in the speech motor network contribute to the cause of stuttering and which differences represent compensation for stuttering.

More recently, an alternative hypothesis has been suggested which explains overactive right frontal activity in PWS as the result of an overactive inhibition network in PWS.

1.4.2 Overactivity in Right IFG

In the first meta-analysis of PET and fMRI studies, overactivity of the right IFG was identified as one of three "neural signatures" of developmental stuttering (Brown et al., 2005). However, the mechanisms involved in this activity remain unclear. Evidence from the field of human executive control shows that the right IFG has a role in inhibiting movements (Aron, Behrens,

Smith, Frank, & Poldrack, 2007; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004; Aron & Poldrack, 2006; Chambers et al., 2007; Hartwigsen, Neef, Camilleri, Margulies, & Eickhoff, 2019; Xue et al., 2008). A recent hypothesis suggests that right IFG hyperactivation could represent an overactive inhibition signal in PWS that causes moments of stuttering (Neef et al., 2016; Neef, Bütfering, et al., 2018).

Recent evidence has attempted to test this hypothesis. One study isolated the time course of rIFG activation during speech in PWS and PWTF (Neef et al., 2016). Compared with left hemisphere regions activated by speaking (including the IFG and temporal areas) the right IFG showed delayed peak activations, corresponding to the end of utterances, for both PWS and PWTF, with stronger peaks in PWS. In addition, the degree of hyperactivity in right IFG correlated positively with stuttering severity (Neef, Anwander, et al., 2018). This would suggest that hyperactivation contributes to stuttering (Neef, Anwander, et al., 2018). Another study recorded fMRI whilst PWS performed a manual GO/NOGO task (Metzger et al., 2018). Compared with PWTF, PWS had increased network synchronization between the right IFG and the globus pallidus and thalamus, respectively.

Whilst the right IFG has been the focus of this recent theory, general movement literature implicates the right IFG as one part of a network of areas involved in inhibitory control, including the SMA and subcortical regions including the basal ganglia and thalamus (Aron et al., 2003; Aron & Poldrack, 2006; Hartwigsen et al., 2019; Xue et al., 2008).

1.4.3 Subcortical Differences

Differences in function and anatomy of structures within subcortical areas are hypothesised to reflect differences in control over the initiation and inhibition of speech movements (Alm, 2004; Bohland et al., 2010; Civier, Bullock, Max, & Guenther, 2013).

The GODIVA model (Gradient Order Directions Into Velocities of Articulators) is an extension of the DIVA model described earlier (Bohland et al., 2010; Guenther, 2016). Within this neurocomputational model of typical speech articulation, each node in the model can be modulated in order to show the effect is has on the output of the model. Disconnection of cortico-striatal pathways as well as a dysregulation of dopamine production within the basal ganglia resulted in stuttering-like output from the model (Civier et al., 2013). This suggests that stuttering symptoms may be the result of aberrant timing of the neural signalling within basal ganglia-thalamo-cortico loops, a theory for which there is substantial evidence.

The communication within these basal ganglia-cortical circuits is modulated via dopaminergic neurons. Two pathways are responsible for the initiation and inhibition of movement: the direct pathway is responsible for initiating action via disinhibition of the thalamic projections to the motor cortex. The indirect pathway is responsible for inhibition of movement by increasing the tonic inhibition of the thalamus and therefore decreasing signalling to the motor cortex. An imbalance between the direct and indirect pathways is hypothesised to result in stuttered moments: stronger indirect pathway activation results in a strong inhibition signal that may overcome any initiation signal from the direct pathway (Alm, 2004).

In addition, it is hypothesised that timing signals are not properly regulated from the basal ganglia to other regions in the brain including the motor cortex, SMA and rIFG (Alm, 2014; Kearney & Guenther, 2019; Max, Guenther, Gracco, Ghosh, & Wallace, 2004). These timing signals are responsible for the initiation of a sequence, the transition from one element of the speech sequence to the next and the inhibition of a speech sound. Differences in the regulation of these timing sequences may result in repetitions or prolongations of sounds (Lu et al., 2010). Accordingly, disfluent states are more likely to occur at the beginning of an utterance (Alm, 2004; Howell & Au-Yeung, 2002; Watkins et al., 2008), at the initiation of the speech sequence.

In support, numerous neuroimaging studies implicate the basal ganglia in developmental stuttering (Giraud et al., 2008; Metzger et al., 2018; Neef, Bütfering, et al., 2018; Watkins et al., 2008). There is evidence for altered functional connectivity between the putamen and the superior temporal gurus and inferior pareital lobules in adults (Yang, Jia, Siok, & Tan, 2016) and children who sutter (Chang & Zhu, 2013). In addition, the amount of activity in the caudate nuclei correlated with stuttering severity (Giraud et al., 2008) and was reduced following therapy (Giraud et al., 2008; Kell et al., 2009) and during fluency-enhanced states, such as choral speech (Fox et al., 1996) and metronome-timed speech (Toyomura, Fujii, & Kuriki, 2011). Structural neuroimaging work also showed bigger volume of the right nucleus accumbens, which is hypothesised to be a motivation-to-movement interface in PWS compared with PWTF (Neef, Bütfering, et al., 2018). However, it is unclear how greater volume maps onto stuttering symptoms as the volume of the nucleus accumbens was not correlated with stuttering severity or psycho-social consequences of stuttering (Neef, Bütfering, et al., 2018).

In addition to imaging studies, pharmaceutical interventions that target dopamine regulation, crucial to basal ganglia function, have shown some positive results. It is important to note however that the following studies are based on small sample sizes and often contain variable results. Dopamine antagonists appear to improve fluency (Lavid et al., 1999; Maguire et al., 2000), whereas agonists worsen fluency (Anderson et al., 1999). This supports an excessive dopamine hypothesis in which PWS produce too much dopamine, which results in failure to initiate a sound via the direct pathway. Further work supports this hypothesis, showing adults who stutter had greater uptake of dopamine in the striatum as well as in cortical auditory processing areas compared with PWTF (Wu et al., 1997). Interestingly, computer simulations using the GODIVA model showed that both increasing *and* decreasing dopamine release from the striatum lead to stuttering-like output of the model (Civier et al., 2013).

Finally, lesions to the basal ganglia can result in stuttering onset (Heuer, Sataloff, Mandel, & Travers, 1996; Ludlow, Rosenberg, Salazar, Grafman, & Smutok, 1987; Tani & Sakai, 2011; Van Borsel, Van Der Made, & Santens, 2003). The uncontrollable nature of natural lesions means that it is difficult to establish causal relationships between a specific structure and stuttering onset. Furthermore, the small size of the structures and their highly complex and inter-connected nature exacerbates this problem. In rare cases, stimulation can be applied to the individual components of the basal ganglia which can provide both accuracy and cause and effect relationships: during surgery in an awake patient, stimulation of the left thalamus resulted in repetition of the initial syllable of an utterance (Ojemann & Ward, 1971). In addition, the sub-thalamic nucleus (STN) has been associated with onset of stuttering following

deep brain stimulation as a treatment for Parkinson's disease (Burghaus et al., 2006), further implicating the basal ganglia in the onset of stuttering.

1.4.4 Summary

Neural differences in PWS are evident in several structures contributing to the function of the cortico-basal ganglia-thalamocortical motor loop involved in the co-ordination of fluent speech. However, finding the root cause of stuttering within this network is challenging due to the interconnected and inter-reliant nature of this complex network.

1.5 Kinematic differences

Kinematic differences between PWS and PWTF are described in detail in a systematic review in chapter 3.

In brief, weaker neural control of speech motor commands can be measured at the level of the articulators. Measuring the precise movements of movements during speech is very difficult due to the speed of the movements and the positioning of the majority of the articulators within the vocal tract. Due to these limitations, the few studies that do measure kinematic movements in PWS vary greatly in their methodology and protocols, making comparison hard. Overall, the strongest evidence suggests that PWS make more variable movements over repeated utterances compared with PWTF. Greater variability is indicative of weaker speech motor control.

1.6 Modulating Speech Motor Control

As discussed, speech and language therapies currently offer limited options for improving fluency in people who stutter in the long term. The ability to use knowledge of the underlying neural differences in PWS to promote the effectiveness of therapy could be of interest to clinicians.

Transcranial direct current stimulation (tDCS) in a non-invasive brain stimulation technique that shows promise in promoting learning in a variety of topics (See chapter 2 for a detailed description of tDCS). A recent randomised control trial (RCT) from our group combined behavioural and neural interventions that targeted the left IFC to increase fluency in PWS (Chesters et al., 2018). For 20 minutes a day over five consecutive days, anodal tDCS was applied to the left IFC whilst PWS performed fluency enhancing behavioural tasks. Compared to a group of people receiving sham stimulation with the behavioural therapy, anodal tDCS led to an increase in speech fluency one week after the five-day intervention. And this improvement persisted at six-weeks follow up. Importantly, this study indicates that tDCS could offer an inexpensive, clinically useful, and efficient tool to increase fluency in PWS.

In order to investigate how tDCS can be used to promote fluency, I aimed to test tDCS and verbal fluency in a large group of typically fluent people. Using a population of typical, fluent speakers enables us to recruit a larger sample than for a clinical population, such as people

who stutter. Furthermore, tDCS can be used to modulate speech motor control in both directions (temporarily improve and worsen) without the risk that we will make fluency worse for a clinical population.

1.7 Aims and Scope of Thesis.

My overarching objective was to investigate speech motor control and speech (dis)fluency. To do this, I used a multi-modal approach to investigate speech motor control from the neural commands to the kinematic output of this system. This was achieved via four strands of work described below. All MRI data (strands two and three) were collected during the baseline session of a large randomized control trial currently ongoing in our research group.

1.7.1 Study 1: Systematic Review

I conducted a systematic review of previous studies of articulation in PWS that used a variety of different methods (Chapter 3). Technological advances over the last 10 years have offered new insight into the speech motor control of PWS by measuring precise movements of the articulators involved in speech. This review has given me a better understanding of the existing literature and forms the basis for my ideas using real time MRI to non-invasively record speech movements of the entire vocal tract.

1.7.2 Study 2: Vocal tract MRI

I then used vocal tract MRI (vtMRI) to look at the speech movements in PWS (Chapter 4). As this is a novel technique, experiments have been designed to first replicate and then extend key results identified via the systematic review that used different methods. This work was collected during the baseline (pre-intervention) session of the RCT.

1.7.3 Study 3: fMRI

I also used functional MRI of the brain to investigate differences in the neural control of speech in PWS and PWTF (Chapter 5). I used a task known as the Stop-Signal task that was previously used to investigate inhibitory motor control in both speech and manual movements (Xue, Aron & Poldrack, 2008). This work was also collected as part of the baseline session of the RCT.

1.7.4 Study 4: tDCS

Finally, to further understand the ways in which speech fluency can be enhanced using brain stimulation techniques, I designed a study to investigate whether tDCS could modulate speech articulation in a typically fluent population (Chapter 6). I used both behavioural and electrophysiological outcomes to assess the role of tDCS in changing performance on a complex articulation task. This work is not part of the RCT.

2 Methodology

A range of techniques were used within this thesis in order to measure speech motor control from brain to kinematics. Magnetic Resonance Imaging (MRI) was used in two different ways: first, I looked at the articulation of speech production using vtMRI (Chapter 4), and then I looked at how the brain controls speech articulation using fMRI (Chapter 5). Finally, I looked at whether we could use what we know about the brain's control of speech movements to modulate speech motor control using brain stimulation (Chapter 6).

In this thesis fMRI is used with standard parameters (chapter 5) and so details of this method will be given in the chapter, only. Here, I cover vtMRI as it is a novel method and brain stimulation techniques because there are many free parameters that require consideration when designing studies.

2.1 Vocal-tract MRI

Recent advances in MRI have enabled us to view and record the dynamic motion of the vocal tract during natural speech production in a non-invasive manner. Prior to this, methods were restricted to measuring one or two articulators at a time and were sometimes invasive. This disrupts the movements and the sensorimotor feedback of the movements which could be particularly problematic for studying developmental stuttering as changes in sensory feedback

can be fluency enhancing. Recent studies that have used these methods to measure the kinematics of speech production in PWS were systematically reviewed in chapter 3. Here, I focus on the use of vocal-tract MRI (vtMRI) to measure speech articulation safely and non-invasively.

VtMRI has been used within the fields of linguistic theory and clinical research. Within the field of linguistic theory, vtMRI has been used to study articulation in different languages (Carignan, Shosted, Fu, Liang, & Sutton, 2015; Teixeira et al., 2012), coarticulation (Demolin, Hassid, Metens, & Soquet, 2002) and consonants in click languages (Proctor et al., 2014). VtMRI has also been used to investigate non-speech events, such as beatboxing (Greer, Blaylock, Patil, & Narayanan, 2018; Proctor, Bresch, Byrd, Nayak, & Narayanan, 2013). Researchers have also used vtMRI to answer important clinical questions. vtMRI has been used to image patients who have undergone glossectomy (partial removal of the tongue) to treat oral cancer (Mády et al., 2003) and in patients with apraxia of speech (Hagedorn et al., 2017).

2.1.1 MRI sequence and data reconstruction

VtMRI uses conventional MRI in a novel way. This requires the help of an MRI physicist to create the sequences for the scanner and then reconstruct the raw scanner data into a video of speech for off-line analyses. Dr. Mark Chiew from the Wellcome Centre for Integrative neuroscience was our collaborator for this project.

Dr. Mark Chiew designed a custom sequence that would capture T1-weighted, mid-sagittal images of the vocal tract at a very fast speed whilst maintaining a good spatial resolution. A common slice time for a brain T1-weighted acquisition is approximately 800 milliseconds with a spatial resolution of 2mm isotropic (3D voxel). The vocal tract images were captured with in-plane spatial resolution of 2mm x 2mm using a radial FLASH sequence with a repetition time of 2.5 milliseconds with golden angle sampling. Images were reconstructed at 33.3 frames per second using a second order spatio-temporal total generalized variation constraint (Knoll et al., 2010). A video of me speaking in the scanner can be found by following the link in Figure 2.1, below.

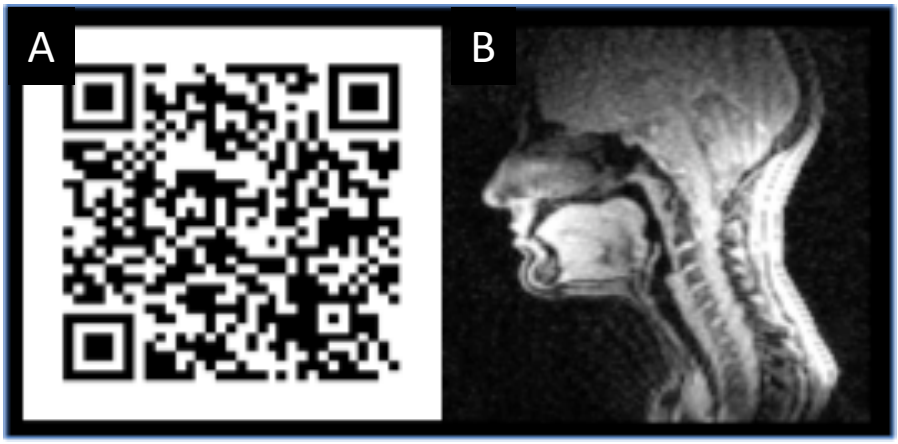


Figure 2.1 Example video of vocal tract imaging during naturalistic speech.
A) Follow QR code for a link to the video. B) A still from the video.

2.1.2 Data analysis

Once the data has been reconstructed into a video, I then measure the movements of the articulators. To do this, I use a custom toolbox (J. Kim, Kumar, Lee, & Narayanan, 2014).

Movement of the articulators is captured using grid-based segmentation. This provides a co-ordinate system that can be superimposed on the images of the vocal tract. First, a line drawn by hand captures the centre of the vocal tract from the lips to the larynx. A grid is then constructed around this line. Each gridline intersects with the midline at a perpendicular angle (see Figure 2.2 B). The middle of the open airway is identified and used as the centre of each gridline such that they will intersect two air-tissue boundaries; the upper and lower boundaries of the midsagittal vocal tract. A curved grid is beneficial as it matches the morphology of the vocal tract and the articulators. For example the velum moves at the same angle as the radial gridlines that overlay it (see Figure 2.2 C).

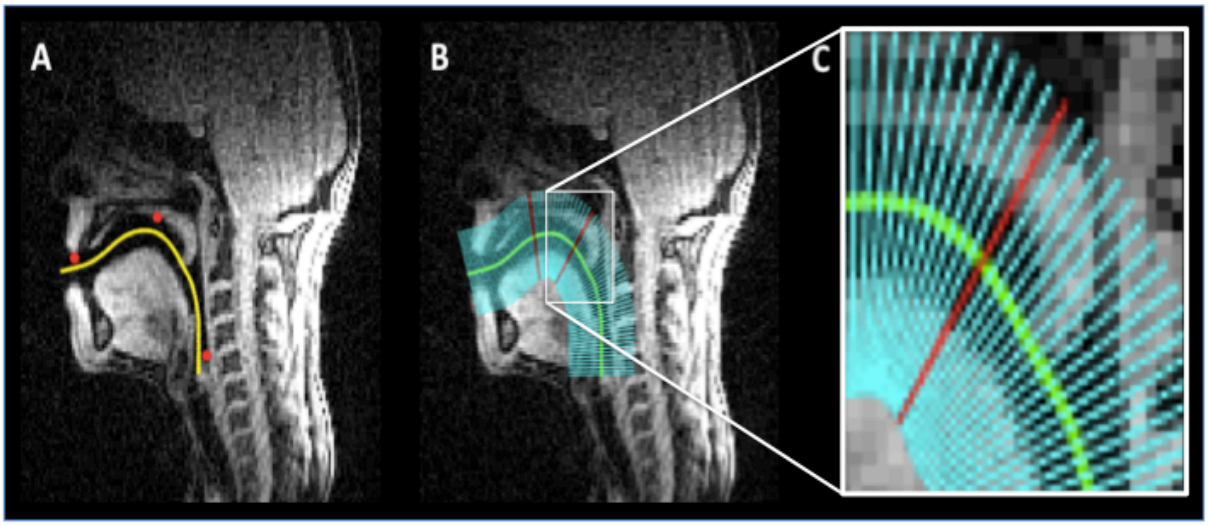


Figure 2.2 Grid-based segmentation of the vocal tract.

(A) Identification of the vocal tract shape (yellow line) and key anatomical landmarks (red dots from left to right: lower point of the upper lip, back of the hard palate and the pharyngeal wall at the level of the larynx) determines the placement of the grid (B). The centre line is smoothed. The gridlines are then placed with an equal distance along the centre line, perpendicular to the line. A close up of this process is demonstrated on the larynx (C).

Once the grid is applied, the intersections between each gridline and tissue boundaries of interest can be tracked based on abrupt changes in pixel intensity (where white pixels representing tissue, meet black pixels representing air).

A number of parameters can be optimised to enable good tracking of the air-tissue boundaries. For example, thresholds for pixel intensity and how large a cluster of similar pixels must be to determine the air-tissue boundary. A balance is required: choosing a high pixel intensity threshold for the lips (must be very white) can help the algorithm ignore ghosting (shadowing due to very fast movements) whereas a low pixel intensity threshold is needed for the hard palate due to the decreased signal from that area.

In addition, interpolation and smoothing is used to fill in the information between grid lines. To minimise the effects of interpolation, it is important that gridlines are spaced closely together (See an example of this in Figure 2.2 A).

Prior to performing analysis in chapter 4, substantial piloting was done in order to achieve the best tracking outcomes for our specific scans. Subsequently, the same parameters were used for every participant scan.

An example of this airway tracking is shown in figure 2.3, below. For analyses purposes, either the movement of each air-tissue boundary or the distance between the two (aperture of the airway) can be measured. Figure 2.3 demonstrates the changes in the aperture of the airway over a repetition of a single nonword. In chapter 6 I use the distance between the upper and lower lips (highlighted in blue) as a variable.

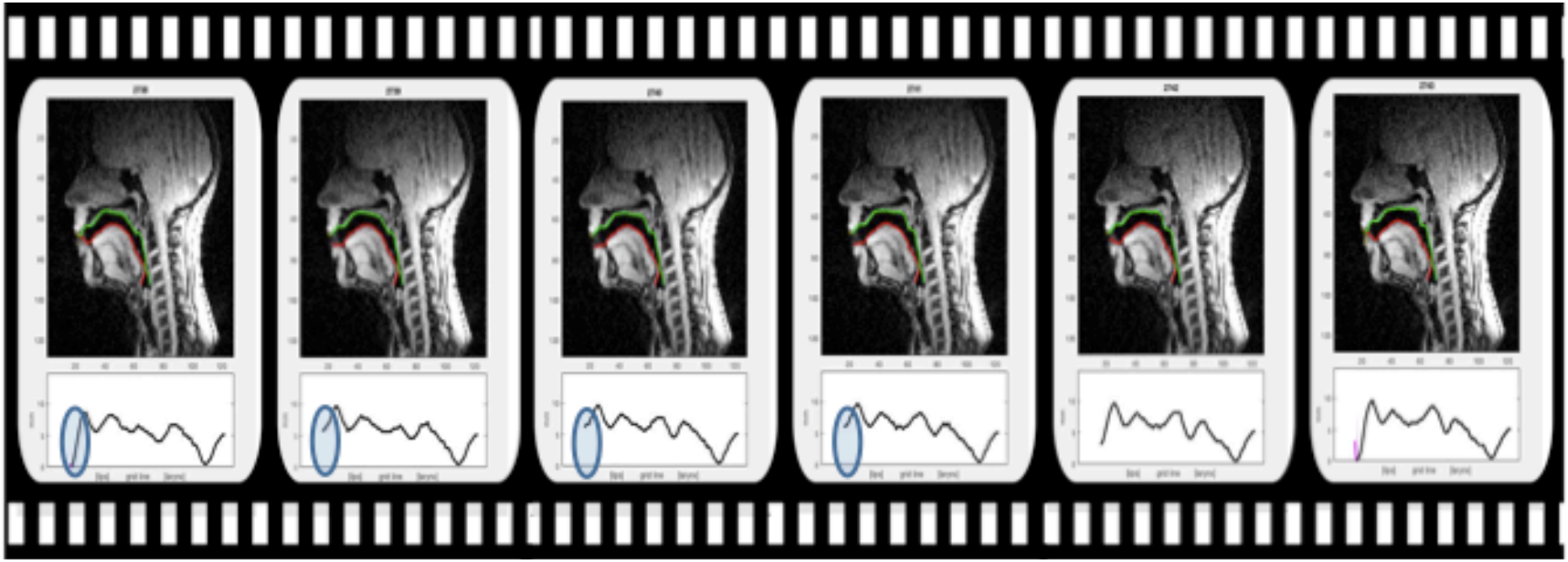


Figure 2.3 Tracking the airway using vtMRI

Frames from one utterance of the nonword 'mab'. Each image is one frame. Bottom panel shows the distance between air tissue boundaries (green and red lines) from the lips (left) to the larynx (right). Our measure of lip aperture (the distance between the upper and lower lips) is highlighted in blue.

2.2 Non-Invasive Brain Stimulation

Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are part of a family of non-invasive brain stimulation tools (NIBS). During tDCS, a constant current of between 1 and 2mA is passed between two electrodes that are in contact with the scalp (see Figure 2.4). Some of this current penetrates through the skull and acts upon the cortex in a polarity specific manner: the anode (positive electrode) up-regulates the cortex, and the cathode (negative electrode) down-regulates the cortex (Nitsche & Paulus, 2000). This can also lead to modulations in behaviour that are relevant to the area of cortex being stimulated (Nitsche et al., 2003; Stagg et al., 2009).

Applying tDCS is safe, portable, easy to administer and is well tolerated by participants. TDCS is a comparatively inexpensive tool to purchase and maintain. The ease of use, combined with the potential to modulate brain and behaviour has lead to a surge of investigations into the usefulness of tDCS in both clinical and typical populations (Clark & Parasuraman, 2014). TDCS appears to show some promise as a useful tool for the treatment of disorders that are often resistant to treatment, including depression (Martin et al., 2018; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009; Sampaio et al., 2018; though see Loo et al., 2018), Parkinson's Disease (Fregni et al., 2006; Machado, 2016) and stroke-induced deficits (Schlaug, Renga, & Nair, 2008).

Figure 2.4 Example tDCS set up.

tDCS electrodes are placed inside saline-soaked sponges and held against the scalp by rubber straps. Here, a bihemispheric design (as used in chapter 6), with the anode (red sponge) placed over the left hemisphere IFG/lip representation of M1 and the cathode (blue sponge) placed over the right hemisphere homologue.

2.2.1 Physiological mechanisms of tDCS

By itself, tDCS does not induce cerebral activity. Instead, it affects the cortex at the sub-threshold level by modulating the likelihood that a neuron will fire by either depolarising (anodal) or hyperpolarising (cathodal) it (Schlaug et al., 2008). Over the course of stimulation, these sub-threshold changes in the neuronal membrane can promote, or depress, longer-term learning mechanisms including modulation of GABAa synaptic circuits. This promotes Hebbian learning mechanisms, such as long-term potentiation (LTP)-like effects on the interneurons of the primary motor cortex (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Muellbacher et al., 2002; Ziemann, Iliać, Pauli, Meintzschel, & Ruge, 2004). These processes

underpin behavioural learning. Therefore, the ability to modulate these processes in order to promote long-term learning in the healthy and disordered brain is of great interest.

2.2.2 Using TMS to measure the effect of tDCS on the cortex

TMS uses electromagnetic principles to stimulate the cortex. The TMS 'coil' contains copper wire, wound repeatedly in a figure of eight. When an electric current is briefly passed through the wire, this sets up a magnetic field that is strongest where the wires cross in the figure of eight. Anything within this rapidly changing magnetic field will be forced to carry a charge. This includes depolarisation of the axons under the coil, up to a distance of 3 cm from the coil. The primary motor cortex (M1) offers an opportunity to study the changes in cortical excitability caused by tDCS because we can use TMS to elicit motor-evoked potentials (MEPs). MEPs are the response elicited in a target muscle by applying a single pulse of TMS over its cortical representation. When a pulse of TMS is delivered, an action potential is created in the peripheral axons that innervate the target muscle. This muscle response can be measured using electromyography electrodes (Figure 2.5 B). The amplitude of the MEP can be used as a quantification of the excitability of the stimulated area of cortex. The latency of the MEP reflects the time it takes for the neural impulses to reach the peripheral muscles so is affected by distance.

Measuring TMS-induced MEPs before and after tDCS applied to the motor cortex can tell us about the changes in cortical excitability caused by the tDCS. Anodal tDCS is predicted to lead to an increase in excitability and therefore an increase in the amplitude of the MEP.

Cathodal tDCS, on the other hand, is thought to reduce cortical excitability, represented by a decrease in the amplitude of the MEP. The process for recording MEPs is demonstrated in Figure 2.5, below.

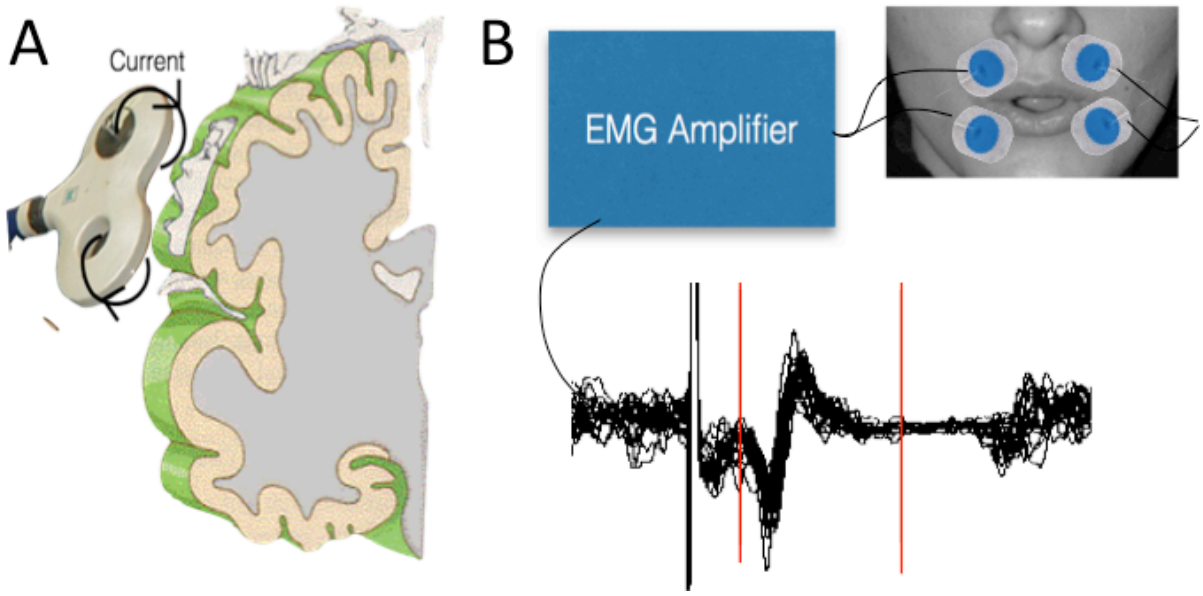


Figure 2.5 Using TMS to elicit MEPs in the lip muscle.

A) A TMS 'coil' is placed over the representation of the lip motor cortex shown on the homunculus. B) The electrical activity of the muscles is recorded using surface electrodes. The average of 20 MEPs from the lip is shown. The vertical black line is the artefact from the stimulation pulse. The peak-to-peak amplitude of the signal within the two red lines (10 to 40 ms) is automatically measured as a quantification of cortical excitability.

TDCS is effective quickly; one minute of 1-mA anodal stimulation led to an increase in MEPs by 40% and cathodal stimulation resulted in a reduction in MEP size by 30% (Nitsche & Paulus, 2000). Furthermore, these changes in MEP sizes are maintained for up to 5 minutes

after 5 minutes of 1mA stimulation (Nitsche & Paulus, 2000). Increasing the amount of stimulation increases the durability of the after-effects. After 13 minutes of 1mA anodal stimulation, the after effects measured by MEPs lasted up to 90 minutes (Nitsche & Paulus, 2001).

2.2.3 Measuring the effect of tDCS on behaviour

The cortical modulation of tDCS has been shown to modulate behaviour. TDCS is most effective when used in combination with a task (Buchwald et al., 2019; Stagg & Nitsche, 2011). Performing a task requires the activation of a network of cortical areas. For example, tapping the finger requires engagement from the hand representation of M1, and premotor cortex. More complex behaviours require a larger network of regions; speech is known to engage the rIFG, motor and pre-motor and supplementary motor areas, as well as more posterior areas (Hickok & Poeppel, 2007). When tDCS is applied to an active area of cortex, the subthreshold modulation of the neuronal membrane acts in unison with the activity caused by performing the task, which together promote learning (Stagg & Nitsche, 2011).

Simple motor tasks combined with tDCS result in polarity specific modulation on behaviour (Antal, Begemeier, Nitsche, & Paulus, 2008; Galea & Celnik, 2009; Reis et al., 2009; Stagg & Nitsche, 2011; Vines, Cerruti, & Schlaug, 2008). For example, a finger tapping sequence task, combined with 1mA anodal tDCS for 15 minutes resulted in shorter reaction times than after sham stimulation (Stagg & Nitsche, 2011). For speech production specifically, there is some evidence to suggest that tDCS can modulate performance in neurologically intact speakers

(Buchwald et al., 2019; Deroche, Nguyen, & Gracco, 2017; Fiori, Cipollari, Caltagirone, & Marangolo, 2014; Lametti, Smith, Freidin, & Watkins, 2018).

Measuring changes in behaviour requires a task that provides room to modulate performance, i.e. participants must not perform at floor or ceiling so that there is room to change performance.

2.2.4 Consolidating tDCS affects on behaviour and cortical excitability

The previous two sections summarise: 1) the effects of tDCS (without a task) on cortical excitability; and 2) the effects of tDCS combined concurrently with a relevant task on behaviour. Limited evidence exists measuring cortical excitability when tDCS is applied concurrently with a task. Bi-hemispheric tDCS (1.5 mA, 10 minutes, with the anode placed over right M1 and the cathode over left M1) paired with a motor learning task, led to a 30% improvement in performance in the left hand (non-dominant, contralateral to anode) and a 69% increase in MEP size (Karok & Witney, 2013). This suggests that MEPs increase after anodal stimulation concurrent with a task. In contrast, a separate study found that anodal tDCS (1-mA, 20 minutes, anode of left M1) applied without a concurrent task increased MEP size as expected but when the stimulation was applied in combination with a motor learning task in the dominant hand, MEP size was not modulated though task performance measurably improved (Amadi, Allman, Johansen-Berg, & Stagg, 2015). The differences in these results may be explained by the differences in stimulation protocol (e.g. 1.5-mA to 1-mA) or the difference in stimulation sites: The brain may respond to stimulation in a different way depending on whether the cortex is functioning optimally (dominant hand; Karok & Witney,

2013) or sub-optimally (non-dominant hand; Amadi et al., 2015). The effect of stimulation protocol on behavioural and cortical outcomes is discussed next.

2.2.5 Variability in tDCS studies

There are many free parameters among which to choose when deciding on a tDCS protocol. Each will affect how the brain responds to the stimulation. I describe each of these in turn.

2.2.5.1 Amount of Stimulation

Different stimulation protocols will contribute to variable responses to stimulation. One factor may be the homeostatic regulation of the cortex in response to different stimulation protocols (Amadi et al., 2015). The brain has evolved to be a highly efficient machine and can regulate firing rate to maintain optimal functioning. This is analogous to sweating in order to cool down when we feel hot. For brain stimulation specifically, if there is too much stimulation delivered to the cortex, homeostatic regulation may cause the brain to act against the stimulation in order to regulate the fine balance of firing required by the brain. There is some evidence in support of this theory; for example, 13 minutes of 1-mA anodal stimulation delivered to the hand representation on M1 (no task) led to an increase in excitability or the cortex, as expected, whereas 20 minutes resulted in a reversal of the response polarity (Monte-Silva et al., 2013). It is therefore important to choose a stimulation protocol that will promote brain function within the bounds of homeostatic regulation.

2.2.5.2 Size of the electrodes

The current density of stimulation must also be considered. Large electrodes deliver stimulation in a more diffuse way compared with smaller electrodes. If using the same amount of stimulation, the current density will be lower for large electrodes compared to small electrodes. Researchers must choose whether to stimulate a large amount of cortex in order to capture a network of areas, or a small amount of cortex to target a specific area. The current density will also affect the sensation at the scalp of the stimulation which may need to be considered if blinding is necessary.

2.2.5.3 Electrode Montage

Most studies use a uni-hemispheric design where one electrode is placed over the region of interest and the other over a region that is assumed to be functionally inert, such as the contralateral sub-orbital ridge, or an extracephalic area such as the shoulder. Some studies use a bi-hemispheric design, in which both electrodes act upon a functionally relevant area of cortex. This is most commonly used when inter-hemispheric inhibition principals are predicted to be beneficial. For example, PWS show underactivity of the left hemisphere and hyperactivity of the right hemisphere IFG. A bi-hemispheric montage, with the anode placed over the left hemisphere to upregulate the cortex and the cathode placed over the right to downregulate the cortex, is predicted to be advantageous.

2.2.5.4 Individual Variability in Response to tDCS

In addition to the above free parameters, there is also variation in the way that individuals respond to tDCS (Wiethoff, Hamada, & Rothwell, 2014). For example, skull thickness,

cerebrospinal fluid thickness and fat content can affect how much stimulation that reaches the cortex (Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015). Modelling current flow based on brain anatomy can help to optimize tDCS in each individual (Bikson, Rahman, Datta, Fregni, & Merabet, 2012; J. H. Kim, Kim, Chang, Kim, & Im, 2013; Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013) but is an expensive option. In addition, homeostatic regulation could be differentially effective for different populations i.e. for an area of brain that is working optimally (such as a healthy brain) compared to an area of brain that is working sub-optimally (such as an area surrounding lesion a site). TDCS may even have variable effectiveness even within a healthy brain; for example, tDCS was shown to be effective at improving a finger sequence task when placed over the representation of the non-dominant hand on M1 but not the dominant hand (Boggio et al., 2006). These factors are important in considering within-population and between-population differences.

3 Systematic Review of Speech Movement Studies in People who Stutter

3.1 Abstract

Introduction: People who stutter (PWS) differ in the neural and kinematic control of their speech. A variety of kinematic measures have been used to explore speech motor control. This systematic review aims to comprehensively evaluate evidence from the last 15 years and consolidate results from studies using these different methods.

Methods: The systematic review followed PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). All articles from 2004-2017 that contained kinematic data of speech in PWS were included. Themes were identified and results were summarised accordingly.

Results: Three themes pertaining to the results of these investigations were identified: variability in speech movements over repeated utterances; the muscular effort involved in speech production; and, the amplitude and duration of speech movements. The evidence consistently showed that PWS were more variable in their speech movements compared with controls. However, findings were inconclusive with respect to whether PWS showed

differences relative to controls in the amount of effort involved in speech production and the size of their speech movements.

Conclusions: The most consistent finding was that PWS showed greater variability than controls. However, the variety of methods employed across different study protocols resulted in the lack of agreement in findings for other measures. Sample sizes were often very small and the reports made use frequently of exploratory analyses rather than hypothesis-driven tests. These factors reduced the power of individual studies to detect differences between PWS and controls. We conclude that future advances in this field of study will only be made if we investigate larger samples with robust measurements.

3.2 Introduction

Speech production is possibly the most complex of human motor behaviours. In one second of fluent speech, we can produce approximately five or six syllables comprising ten to twelve phonemes and a variety of articulatory gestures. This requires coordinating dozens of muscles, from the diaphragm and rib cage, used to expel air through the larynx, to the tongue, lips, and jaw, which are used with precision to shape the chambers in the vocal tract. Over the last 15 years, technological advances have enabled the measurement of precise speech movements with high temporal and spatial resolution. Kinematic analysis of speech movements can offer insights into the control of the speech motor system beyond that of acoustic analysis (Howell, Anderson, Bartrip, & Bailey, 2009; Max & Gracco, 2005). These methods were implemented in the investigation of speech motor control in developmental stuttering. The purpose of this systematic review is to survey the literature published over the last 15 years with a view to reaching a consensus on the findings of these investigations.

3.2.1 Developmental Stuttering

Developmental stuttering, is characterised by speech dysfluencies including repetitions and prolongations of speech sounds as well as temporary failure to initiate speech sounds, known as 'blocks'. Secondary characteristics, including muscular tension accompanying moments of dysfluency and psychosocial consequences of living with a stutter, such as anxiety are also common. Developmental stuttering is first identified in early childhood and affects 5% of children (Andrews & Harris, 1964). Spontaneous recovery is common, resulting in 1% of the adult population continuing to stutter (Yairi & Ambrose, 2013). Contrary to earlier

interpretations of stuttering as a consequence of anxiety or trauma, the contemporary view of developmental stuttering is a speech motor disorder with a distinct neural profile.

3.2.2 Neural control of speech of PWS

Meta-analyses of brain imaging studies revealed key 'neural signatures' of speech motor control in PWS (Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014), although it is unknown which of these are a causal feature of developmental stuttering and which are a consequence. The motor control network, comprising the basal ganglia, cerebellum, inferior frontal gyrus (IFG), medial and lateral premotor cortex, and primary motor cortex, is critically involved in motor planning, execution, and integration of sensory signals for speech production. PWS show a consistent profile of abnormal activity in this network during speech production (Brown, 2005; Watkins, Smith, Davis & Howell, 2008). Structurally, there is reduced white matter integrity underlying the ventral premotor cortex (Chang, Synnestvedt, Ostuni, & Ludlow, 2010; Connally et al., 2014; Sommer, Koch, Paulus, Weiller, & Büchel, 2002; Watkins et al., 2008) and elsewhere in the brain (Neef et al., 2015). Such disruption could impair connectivity between key structures in the speech motor control network, which would lead to reduced integration and poorer timing of the sensorimotor commands that are required for effortless, fluent speech (Neef et al., 2015).

3.2.3 Kinematic control of speech in PWS

Researchers can either directly measure speech kinematics or they can measure differences in the acoustic signal as a proxy for kinematics. The assumption is that different kinematics

will likely lead to differences in the acoustic signal; however, this is not necessarily true, as there is a many-to-one mapping of articulator positions to acoustic consequences (Perkell, Matthies, Svirsky, &; Jordan, 1993). Acoustic measures may not be sensitive to variation in the very fine control of the many muscles involved in speech production. This may be particularly important given that the majority of speech produced by PWS is perceptually fluent.

Unlike for kinematic analysis of trunk or limb movements, most speech articulators are inaccessible for standard recording techniques. Therefore, a variety of methods is required to capture articulator movements during speech, each suited to tracking different articulators. Perhaps the most common technique is electromagnetic articulography, in which small sensors are glued onto the lips, tongue, and (rarely) velum. Participants then sit in a magnetic field, and the positions of the sensors are tracked in three-dimensional space. Similarly, infrared light emitting diodes (IREDs) track movements from sensors placed on the skin (most commonly lips). Ultrasound places a probe beneath the jaw and is used to visualise tongue movements. Electromyography is used also to measure the excitability of the muscles involved in speech (i.e. the power of muscle contraction). A more detailed description of each method is provided in Table 3.1.

Table 3.1 Techniques that measure articulatory movement.

Method	Description of Use	Sampling Rate (Hz)	Articulators
Infrared light emitting diodes (IREDs)	Small (~5mm diameter) infrared light emitting diodes (IREDs) are attached to the skin. An Infra-red camera tracks movement in 3D.	250	Lips and Jaw
Electromagnetic articulography (EMA)	Small (~3mm diameter) sensors coils (with protruding wires) are placed on the surface of the articulators. Low field-strength electromagnetic fields are used to measure the position of the sensors.	500	Lips, tongue and sometimes velum
Ultrasound	Air-tissue boundaries detected using ultrasound. Probe placed on the chin.	50-300	Tongue
Electromyography (EMG)	Gel-backed electrodes (20-60mm diameter) record the electrical signals from muscles during speech.	20-500	Lips

3.2.4 Theories of motor control in PWS

The kinematic differences found between PWS and PWTF have been considered in the context of a number of different theories to account for the dysfluencies characteristic of developmental stuttering. The Speech Motor Skill hypothesis claims that PWS have reduced skill in motor control compared to PWTF (Namasivayam & Van Lieshout, 2011; Peters, Hulstijn, & Van Lieshout, 2000; Van Lieshout et al., 2004). This theory suggests that learning to speak is akin to other fine motor skill learning such that expertise and automaticity are achieved through a combination of innate skill and practice. As with other skills, proficiency varies within a population creating a continuum from poorly to highly skilled. In the case of stuttering, it is suggested that PWS are at the lower end of the skill continuum. Thus, despite everyday 'practice', PWS remain less skilled at producing the precise movements involved in the motor control of speech. This lack of control should be evident during perceptually fluent speech and may contribute to stuttered moments. As with other fine motor skills, (e.g. handwriting, playing a musical instrument or sport), the Speech Motor Skill hypothesis predicts that weaker speech motor skill would result in larger, more effortful, and more variable movements.

Other theories implicate differences between PWS and PWTF in the way that we make predictions about the sensory-motor consequences of our movements (i.e. what we think we should experience if we get the movement right) and how deviations from the target movement (errors) are dealt with. Figure 3.1 shows how breakdowns within this process could contribute to stuttering. The integration of sensory and motor commands is the focus of feedback-based theory of stuttering (Max et al., 2004). This theory proposes that children who stutter have greater difficulty updating the sensory motor predictions of how their articulators will move

(feedforward) in response to error signals (feedback) (number 1, Figure 3.1). In turn, less accurate motor plans create more error signal. Together, this results in difficulty producing stable speech-motor commands. This is hypothesised to result in the pauses, repetitions and prolongations characteristic of stuttered moments.

Alternatively, unstable feedforward models may result in an inappropriate model to which error signals can be compared (number 2, Figure 3.1). Thus, regardless of the accuracy of the motor response produced, the error signal is unable to accurately map onto the predictions generated by the internal model. This mis-match in signal could result in repetitions or pauses in motor execution until the signal is deemed to match. As a consequence, PWS would aim to boost the amount of feedback available in order to gather more information for the processing and integration of afferent signals. Evidence in support of this theory is provided by studies showing that PWS are slower to initiate movement (Bloodstein, 2006; Gilbert & Hillman, 1977) and make slower movements (Caruso, Abbs, & Gracco, 1988). Furthermore, therapies that aim to slow down speech appear to be effective at increasing fluency.

Others (Civier et al., 2010) claim that the greater reliance on feedback leads to an oversensitivity to production errors, which results in unnecessary correction (number 3, Figure 3.1). Finally, a combination of these possibilities could contribute to stuttering, for example, unreliable feedback (3) could cause a failure to update internal models (1) (Daliri, Wieland, Cai, Guenther, & Chang, 2018).

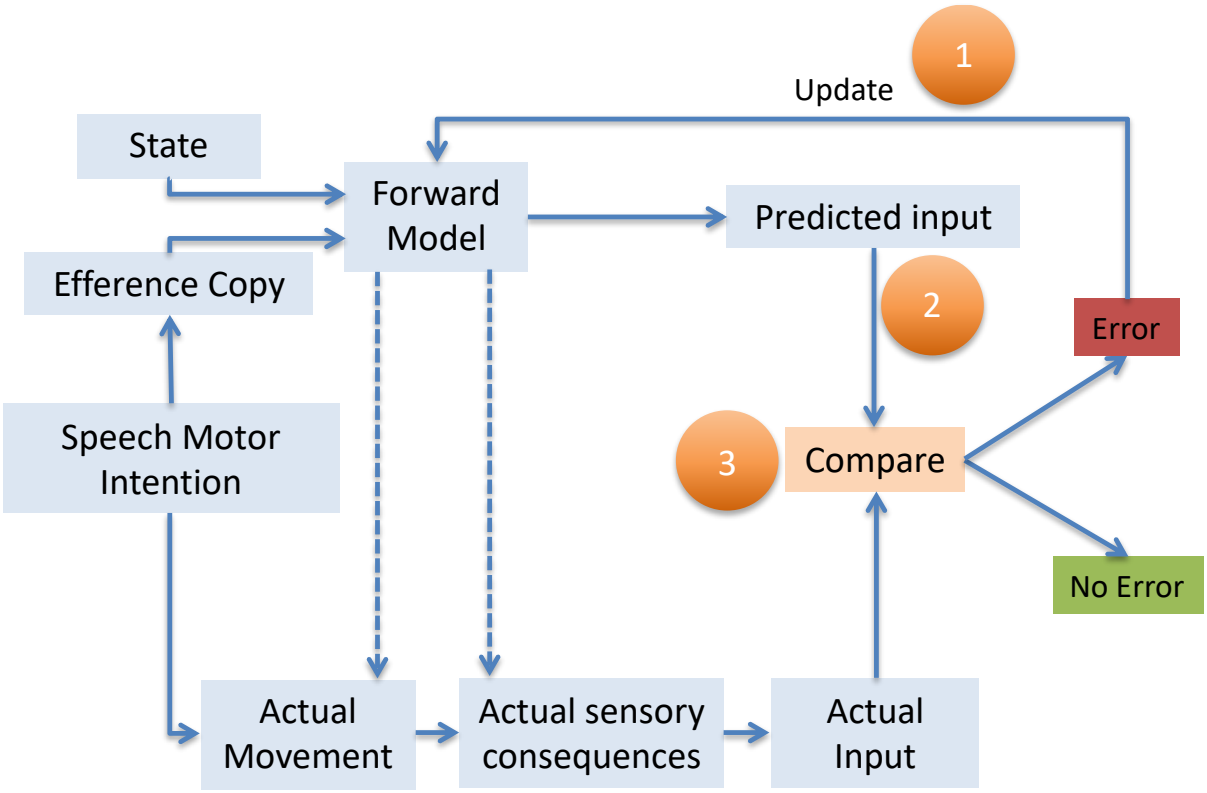


Figure 3.1 Internal models of speech processing.

The predicted sensory-motor consequences of the intended speech are compared against the actual movement. If there is a discrepancy, an error signal is created. The prediction is then updated. Numbers refer to areas within this process that may breakdown and contribute to stuttering (see text).

The literature assessing speech motor control in PWS has been summarised previously (Max et al., 2004; Namasivayam & Van Lieshout, 2011; Van Lieshout et al., 2004) but no systematic review has been carried out. Since these summaries, there have been many more studies of kinematic movement in PWS that aimed to test the hypotheses generated by the above theories. In addition, technology has evolved to capture speech at higher temporal and spatial resolution. The numerous techniques available to study the articulators during speech offer the opportunity to capture the speech motor control system in a variety of ways; however, it makes comparison among studies difficult. The variety of dependent measures combined with the wide variety of

techniques renders a meta-analysis impossible. A systematic review, as presented here, is best suited therefore to provide a comprehensive summary of the results.

This review follows PRISMA guidelines in order to qualitatively compare different measures of articulator movement during speech in PWS in a systematic way. The aim is to summarize the findings of studies that have measured articulation in developmental stuttering following on from a previous literature review in 2004 (Van Lieshout et al., 2004).

3.3 Methodology

3.3.1 Search Strategy

A search was conducted of papers in PubMed and Web of Science published between 2004 and 2017 that included the terms "kinemat*", "movement*", "motion*", "articulat*", "articulography" and "stutter*" or "stammer*".

The selection process is illustrated in Appendix 1. After accounting for duplication of results, 246 papers were identified. Subsequently, abstracts were excluded if they failed to meet the following criteria.

Criteria for exclusion (number excluded in parenthesis)

1) Not available in English (0)
2) Not a journal article (15)
3) Review or Meta-Analysis (22)
4) Non-Human Study (2)
5) Case Study (4)
6) Brain Measure only (21)
7) Main focus not Developmental Stuttering (38)
8) Survey report (6)

This left 138 articles to be assessed based on their full text. Of these, 107 papers were excluded (see PRISMA flow diagram for reasons, Appendix 1). After these exclusions, 31 papers were eligible for the systematic review.

At each of these stages, papers were assessed for eligibility by two independent researchers. At the full-text review stage, inter-rater reliability was 96.2% using an interclass correlation. Any discrepancies were discussed, and a mutual decision made as to whether the papers were included in the systematic review.

Eligible papers are listed in Appendix 2 alongside a summary of the participant sample, methodology and main results.

3.4 Results

Three main themes emerged from our systematic review of the 31 papers. These were studies that focussed on measurement of:

1) variability of motor movements;
2) motor excitability of articulators;
3) amplitude and duration of speech movements.

We summarise the findings for each of these themes below, providing first a short theoretical background to the investigations, then a brief description of the methodology, followed by a synthesis of findings based on our systematic review. Each of the 31 papers selected is cited at least once.

3.4.1 Theme 1: Variability of motor movements

3.4.1.1 Background

Variability of movements over repeated utterances is interpreted as an index of the stability of the speech motor control system. Greater variability indicates reduced control over the articulators. Therefore, PWS are predicted to have greater variability in their speech movements relative to PWTF when measured over repeated utterances of the same target stimulus.

An early study measured variability in the speech of PWS using method aimed at capturing variability across repeated utterances known as the spatio-temporal index (Smith, Goffman, Zelaznik, Ying, & McGillem, 1995). On the basis that PWS have unstable speech motor control relative to PWTF, it was hypothesized that PWS would have greater variability and that this would increase as demands on the speech motor system increased, for example with greater complexity. Furthermore, the speech motor skills hypothesis (Peters et al., 2000) claims that PWS are resistant to long-term learning of speech motor control, so it was predicted that variability would reduce over repetitions in the short term but return to baseline levels over a longer term. The results supported these predictions: PWS were more variable than PWTF, and variability increased as the linguistic complexity (but not length) of the target utterance increased (Kleinow & Smith, 2000).

3.4.1.2 Methods

Variability in measures of movement over space and time can be captured in a number of ways. The most commonly used in the literature reviewed was a measurement known as the spatio-temporal index (STI; Smith et al., 1995). The STI normalises measures of articulator movement in both time (duration) and space (for example, lip aperture) to create a single measure of variability (Smith et al., 1995). The position of an articulator in space (or difference between the positions of two articulators) is tracked over time to produce a 2-D trace of the movement. For each subject, the amplitude of movements are normalised using a z transformation and the duration of the movements are normalised by equating the x-axis of the trace in terms of the number of units of time. The standard deviation of the amplitude measurement across the aligned traces for repeated utterances is measured at small time intervals (e.g. 2% bins of total duration (Kleinow & Smith, 2000) and summed to produce a single index of variability. The

cyclic STI is an adaptation of the STI that aims reduce the amount of variability attributable to utterance-length influences. Rather than normalising across an entire utterance, the cSTI normalises for each movement cycle; the peak-to-peak segment of a trajectory of an opening or closing movement (e.g. jaw).

3.4.1.3 Results

(i) general findings

The STI was used by many studies in our review period (Ambrose, Yairi, Loucks, Seery, & Throneburg, 2015; Howell et al., 2009; Jackson, Tiede, Beal, & Whalen, 2016; MacPherson & Smith, 2013; Sasisekaran, 2013; Sasisekaran & Weisberg, 2014; Smith, Goffman, Sasisekaran, & Weber-Fox, 2012; Usler, Smith, & Weber-Fox, 2017; Walsh, Mettel, & Smith, 2015). In addition, the cyclic STI is used in a smaller number of studies (Namasivayam & van Lieshout, 2008; Namasivayam, van Lieshout, & De Nil, 2008; Van Lieshout, Ben-David, Lipski, & Namasivayam, 2014).

The results of the studies reviewed provide strong evidence for the finding that PWS produce perceptually fluent speech with greater variability over repeated utterances compared with controls. PWS were more variable than controls when producing near and far targeted jaw movements (Loucks & De Nil, 2006b, 2012; Loucks, De Nil, & Sasisekaran, 2007), vowel sounds (Frisch, Maxfield, & Belmont, 2016), simple (Sasisekaran, 2013) and complex nonwords (Smith, Sadagopan, Walsh, & Weber-Fox, 2010), and simple sentences (Howell et al., 2009; Jackson et al., 2016).

Even though the majority of studies reviewed reported that PWS had greater variability in speech movements, it is worth noting that there was a small number of studies where no difference between PWS and PWTF was found (Max & Yudman, 2003; Namasivayam, van Lieshout, McIlroy, & De Nil, 2009; Sasisekaran & Weisberg, 2014; Van Lieshout et al., 2014). Also, a couple of studies reported only a non-significant trend towards group differences ($0.05 < p < 0.065$; Ambrose et al., 2015; Namasivayam & van Lieshout, 2008).

(ii) effects of task demands on variability measurements

Several studies aimed to investigate how tasks make greater demands on the speech motor system and whether this would differentially impact on measurements of variability in PWS. For example, one study recorded lip aperture using IREDs in a group of PWS and PWTF as they repeated nonwords that increased in length (from one to four syllables) and linguistic complexity (Smith et al., 2010). Results showed an interaction between group and stimuli, such that variability increased to a greater degree than PWTF as the utterances became more complex (Smith et al., 2010). This finding is partially supported by a similar study that used six and eleven syllable nonwords (without control of linguistic complexities) and found a non-significant interaction between group and nonword length, such that PWS produced the 11 syllable nonwords with greater variability than the six syllable nonword, but PWTF did not (Sasisekaran, 2013). However, in one study of children who stutter, this pattern was reversed; children who stutter produced more variable movements than children who do not stutter during production of simple sentences, but the groups did not differ during production of syntactically complex sentences (MacPherson & Smith, 2013). Whereas the control group repeated complex sentences

with a higher variability index than simple sentences, the children who stutter had high variability indices for both simple and complex sentences. Overall, these results suggest that length of utterance and complexity increases variability in all speakers, but that PWS may be more affected than PWTF.

The rate of speech being produced is thought to increase demands on the speech motor system. One study found evidence that increasing speech rate increased the variability of lip movements for PWS and PWTF but the two groups were not differentially affected (Namasivayam & van Lieshout, 2008).

Generally, PWS and PWTF are likely to make more errors when speaking under socio-cognitive stress, such as in front of an audience (Alm, 2014). Two papers reviewed assessed the effect of social and emotional stress on speech motor control in PWS. In a relatively large sample (20 per group), the STI of PWS was greater than PWTF when speaking alone in front of an experimenter but when two observers were added to the room, PWS reduced in variability and variability in PWTF was unchanged (Jackson et al., 2016). The authors suggested that PWS reduced the variability in their speech in order to maintain levels of fluency when under greater socio-cognitive stress. In contrast, another study found no difference between PWS and PWTF in the variability of lip movements during production of neutral words or those with stuttering-specific emotional content (e.g. 'audience') (Van Lieshout et al., 2014). Taken together, it seems that socio-cognitive stress affects speech motor control in unexpected ways and that there is preliminary support that it serves to reduce variability in perceptually fluent utterances while also increasing the likelihood of dysfluency.

(iii) effects of practice on variability

According to the speech motor skills hypothesis, PWS should reduce the variability of their speech movements over a short period of practice but this improvement is temporary and variability will return to baseline levels over the longer term (Peters et al., 2000). Several studies showed that, over the course of repeated utterances, the variability of movements reduced for PWS but remained stable for PWTF (Namasivayam & van Lieshout, 2008; Sasisekaran & Weisberg, 2014; Smith et al., 2010). For example, in PWS, the variability over the first five repetitions of a nonword was significantly larger than for the second five repetitions, but variability was unchanged for PWTF (Smith et al., 2010). Another study found that the size of the practice effect was negatively correlated with the severity of stuttering, suggesting that PWS with greater severity did not benefit as much from practice compared with those with lower severity (Sasisekaran, 2013). As predicted, the short-term reduction in variability with practice did not extend to the longer term; when tested a day later, the STI scores of PWS that had reduced across repeated utterances returned to levels comparable with the start of the first session (Namasivayam et al., 2008). In sum, practice can reduce the amount of variability in the speech movements of PWS in the short-term, particularly in those who with milder stuttering severity but these effects are temporary.

(iv) comparison of kinematic and acoustic variability

Measuring variability using the STI requires a movement trace to be captured at a high temporal and spatial resolution. To date the method has been used with expensive and labour-intensive techniques, including EMA, IREDs and ultrasound. The ability to capture variability indices from the acoustic output instead would offer a more inexpensive alternative. The STI method

was applied to the speech envelope and compared with kinematic data collected using EMA (Howell et al., 2009). PWS had more variability over repeated utterances of simple sentences compared with PWTF in both the acoustic and the kinematic measures, which were also strongly correlated. Nevertheless, the amount of variance accounted for with each method was 17% for the acoustic analysis and 53% for the kinematic one. This difference may reflect different sensitivities in capturing variability by the two methods, or that the kinematic data measures variability by the lips only rather than the product of variability across the whole vocal tract in the acoustic data. The similarity of results from the acoustic and kinematic measures provided evidence to suggest that variability is similar across different articulators in the whole vocal tract but requires confirmation from measurement of these other articulators.

(v) Critique

Sample sizes for many of the studies reviewed here were typically small (less than 10 PWS) and this was true of those with and those without significant group differences. The within group variance in the STI was typically larger for PWS than PWTF (Usler et al., 2017). For example, in a vowel repetition task, many PWS had mean levels of movement variability within the range of PWTF, with only seven out of 23 PWS performing more than two standard deviations above the group average of PWTF (Frisch et al., 2016). This between-subject variance at the group level further reduced the power to detect a difference between groups. As some PWS produced speech that varied to the same extent as PWTF, it is difficult to conclude that increased variability of speech movements is a key characteristic trait of PWS. Rather, there may be subgroups of PWS for whom variability is characteristic of their speech movement control.

3.4.1.4 Summary

Across the studies, there was support for the following findings: PWS make more variable articulator movements than their fluent counterparts over repeated movements of perceptually fluent utterances; within PWS, variability increased as a function of task demands, such as increased phonological complexity and speech rate; and, PWS show short-term benefit of practice, with variability decreasing over the course of the repeated utterances. Even though the majority of published findings support the notion that PWS show greater variability in their speech movements and hence have weaker speech motor control, larger sample sizes are needed to address the heterogeneity seen in the smaller samples studied thus far.

3.4.2 Theme 2: Motor excitability

3.4.2.1 Background

According to the Speech Motor Skill hypothesis (Peters et al., 2000), highly automatic, learned movements are energy efficient. Therefore, those predicted to have weak speech motor skill, such as PWS, would have high-energy costs associated with more effortful movements compared with fluent speakers.

3.4.2.2 Methods

Measuring the excitability of the muscles involved in speech has been used to infer the amount of effort needed for production. Electromyography (EMG) measures the electrical activity of a

muscle via electrodes placed on the skin covering the muscle. It is difficult to place electrodes on articulators inside the vocal tract, such as the tongue. Therefore, the EMG studies reviewed here were typically limited to capturing the excitability of the lips.

3.4.2.3 Results

Overall, the literature reviewed did not support the prediction made by the Speech Motor Skills hypothesis, namely that PWS have more effortful movements than PWTF. PWS had higher EMG amplitude of the lips (electrode placed over the centre of the upper and lower *orbicularis oris* muscle) during rest but no group difference during fluent speech (De Andrade, Sassi, Juste, & De Mendonça, 2008). These results are hard to reconcile. Greater activity during rest would indicate a base level of over-activation of the motor signals, but it is not clear why this would not also occur when the muscles are engaged in speech movements. In another study by the same group (De Andrade et al., 2008), PWS were found to have lower excitability of the lip muscles (same electrode placement as above) relative to PWTF during a sequence repetition task (repetition of 'pa-pa...' and 'pa-ta...'). In accordance, PWS also had lower EMG amplitude of the lip muscles (electrodes placed centrally) compared with PWTF when performing lip exercises, such as lip pursing and retraction (de Felício, Freitas, Vitti, & Regalo, 2007). Finally, one study reports no difference in lip muscle excitability between children who stutter and children who are typically fluent during fluent conversational speech and simple sentence repetition (Walsh & Smith, 2013). These results were not predicted by the Speech Motor Skill hypothesis which claims that PWS would make more effortful movements during speech. We conclude therefore that stuttering trait is not associated with abnormal muscle activity within the speech-motor system.

We turn now to the stuttering state. One study found no difference in speech reaction time between PWS and PWTF, but for the PWS, slower reaction time was associated with greater excitability of the lip muscles (De Andrade et al., 2008). It is possible that longer reaction times were the result of undetected dysfluency, which required greater muscular effort. It is worth noting, however, that the sample size was quite small in this study (n=11 per group) and the failure to detect dysfluency means such a conclusion is speculative. A larger study, with an impressive sample size of preschool children who stutter (n= 63) found lower EMG amplitude during dysfluent compared with fluent speech (Walsh & Smith, 2013).

EMG was also used to provide an indirect measure of the lateralisation of the neural control of speech. EMG electrodes were placed on the left and right sides of the upper or lower lips or both to indirectly measure the activity of the contralateral cortical areas that control these muscles. As speech is typically lateralised to the left hemisphere, measurements from the right side of the lip would be expected to be more active during speech movements. Neuroimaging work suggests that PWS do not show the same pattern of lateralisation and are likely to show a more bi-hemispheric activation profile during speech (Kell et al., 2009; Sato et al., 2011; Watkins et al., 2008). If PWS have reduced cerebral lateralisation of speech then the expected asymmetry in muscle excitability for the left and right side of the lips should be reduced. Two studies investigated lateralisation differences and found different results (Choo, Robb, Dalrymple-Alford, Huckabee, & O'Beirne, 2010; Walsh & Smith, 2013). One study recorded EMG from both sides of the upper and lower lip muscles during word and sentence production and lip pursing. The highest EMG amplitude was recorded from the left lower lip of PWS, interpreted as greater right-hemisphere participation in speech production. In PWTF, however, the highest

EMG amplitude was recorded from the right lower lip which was interpreted as greater left-hemisphere participation (Choo et al., 2010). These results were consistent with the prediction that PWS have the reversed pattern of lateralisation compared with PWTF. However, these results were based on just five participants per group. Furthermore, the results were based on the raw EMG signal and were not normalised by participant. This is problematic as the EMG signal can be affected by numerous factors, such as amount of residue on the skin, and amount of fat content under the electrode (Stepp, 2012). Inspection of the individual data revealed that one person from the stuttering group drove this effect with particularly high raw EMG signal across all tasks whereas the other four PWS had measurements within the range of PWTF. In a study of EMG signal lateralisation with a much larger sample of children who stutter (n = 63), no differences were found between those who stutter and those who are typically fluent. Further study is required in an adequate sample of adults who stutter to determine whether differences between PWS and PWTF might emerge over the course of development.

3.4.2.4 Summary

In summary, the hypothesis that excitability of the speech motor system is abnormal in developmental stuttering was not supported. It remains unclear how motor excitability relates to dysfluent speech. One study with a large sample size was available for children who stutter, but there is currently no equivalent sample of adults who stutter who have been studied in the same way.

3.4.3 Theme 3: Amplitude and duration of speech movements

3.4.3.1 Background

Theories of stuttering propose that PWS have impairment integrating auditory and somatosensory feedback with ongoing motor control and suggest that producing larger, slower movements would generate more sensory feedback, which could in turn be used to gain better control over speech movements. Conversely, smaller, quicker movements would reduce the amount of feedback available, resulting in poorer integration of sensory-motor signals and poorer speech motor control (Namasivayam & Van Lieshout, 2011). The causal direction of the relationship between movement size and speech motor control is unknown. It may be that PWS have weaker speech motor control because they make smaller, shorter movements, thus generating insufficient feedback. Alternatively, PWS may make larger, slower movements, representing a compensatory mechanism to gather larger feedback information compared to PWTF (Watkins, Chesters, & Connally, 2016).

3.4.3.2 Methods

Several studies measured the amplitude and duration of articulator movements for the lips and jaw in PWS. Dependent variables included the vertical distance traveled by the lower lip and jaw from a resting position or the maximum aperture between the upper and lower lips within an utterance. Movement duration, the time it takes to produce either one specific speech movement or many within an utterance, was also measured.

3.4.3.3 Results

In a large study of 58 children who stutter, boys who stutter were shown to have smaller movement ranges of the lower lip and jaw compared to controls. Girls who stutter showed no differences relative to their fluent controls (Walsh et al., 2015). Similarly, adults who stutter had smaller ranges of movement of the upper lip compared with controls when repeating simple phrases (Van Lieshout et al., 2014). The low number of participants and large number of measurements (10 PWS, nine variables) in the latter study should be noted, however. Furthermore, a different study, similarly underpowered (five PWS), found the opposite pattern of results, namely that PWS made considerably larger and slower lower lip movements compared with controls when repeating simple bi-labial nonwords at both normal and fast rates (Namasivayam & van Lieshout, 2008).

A number of studies found that movement durations during speech production were equivalent in PWS and controls. During sentence repetition, one study measured duration and timing of movements and among the 40 different comparisons made between PWS and PWTF, found that PWS made both quicker and slower movements than PWTF under different conditions (McClean, Tasko, & Runyan, 2004). No overall differences between PWS and PWTF were detected for movement duration in adults (McClean & Tasko, 2004; Smith et al., 2010) and children (Smith et al., 2012; Usler et al., 2017) in studies with much larger samples (>30 PWS). One study assessed the effect of speech therapy on lip movement amplitudes and durations (Tasko, McClean, & Runyan, 2007): compared to baseline, PWS made smaller, quicker movements after successful therapy that reduced their stuttering severity. However, it was unclear

whether the reduction in movement size was the result of better compensation or reflected the reduction in stuttering severity.

Several studies also examined the effect of stressing the speech motor system on movement size. The findings were equivocal. Whilst PWS performed similarly to controls on measures of duration and amplitude during a simple sentence reading task, PWS made larger, slower movements compared with PWTF when asked to speak at a fast rate (Namasivayam et al., 2008). Conversely, adding emotional stress to simple tasks (classic Stroop task, adapted to include words associated with stressful aspects of stuttering) led to a reduction in lip movement amplitude in PWS, but not in PWTF (Van Lieshout et al., 2014). The authors suggested that during stress, PWS restrict their movement in order to maximize the likelihood of fluency. This interpretation is counter to the idea that PWS make larger movements in order to increase the amount of proprioceptive feedback available to them, which in turn might aid fluency.

The extent to which a speaker relies on feedback to produce accurate movements can be assessed by disrupting proprioceptive feedback during speech production. Proprioceptive feedback was disrupted in a group of PWS (n = 9) and PWTF (n = 12) during a sentence repetition task (Loucks & De Nil, 2006a). Applying vibration to the masseter tendon (to disrupt proprioception of jaw movements) led to smaller movement amplitudes in both PWS and PWTF, but these changes did not differ between groups. In another study, PWS and PWTF were compared on their ability to compensate for a bite-block perturbation (Namasivayam et al., 2008). The application of a physical constraint to an articulator (e.g. a bite block) disrupts both the production of speech and the associated sensory feedback. Time and practice are required

to learn the compensatory movements needed to produce the target speech sound (McFarland & Baum, 1995). Theoretically, if PWS have weaker speech motor control, they may take longer to learn to adapt to the perturbation of an articulator. However, no differences between PWS and PWTF for practice effects subsequent to an articulator perturbation were found (Namasivayam & van Lieshout, 2008). Both PWS and PWTF increased movement duration and amplitude during a bite-block perturbation, indicating that both groups found it difficult to compensate (Namasivayam et al., 2008).

3.4.3.4 Summary

Evidence for differences in the amplitude and duration of speech movements of PWS and PWTF are limited. For studies that do report group differences, there is little agreement regarding the direction. Many studies reported large within group variance, particularly for PWS. This, coupled with small sample sizes and many dependent variables increase the likelihood of spurious results.

3.5 Summary and conclusions

We systematically reviewed the literature on speech movement studies in people who stutter. The systematic review followed PRISMA guidelines. All articles from 2004-2017 that contained kinematic data of speech in PWS were assessed. Of these, 33 publications were selected for in depth review. These were grouped to address three themes: variability in speech movements

over repeated utterances; the muscular effort involved in speech production; and, the amplitude and duration of speech movements. Most support was found for greater variability in the speech of PWS compared to PWTF. Support for the other themes was limited as there were only a few studies and many used small sample sizes with a large number of variables.

The most consistent finding among the studies reviewed here was that PWS have greater variability of speech movements across repeated utterances of the same stimulus even when these utterances were perceptually fluent. Such variability is indicative of poor trait-level speech motor control. Findings from this body of work are consistent with one of the predictions of the Speech Motor Skill hypothesis, namely that PWS are resistant to long-term learning of speech motor control. However, the Speech Motor Skills hypothesis makes a number of other predictions for which there was more mixed support. For example, there was no clear evidence to support a difference between PWS and PWTF in levels of muscular effort during rest (trait), speech (state) or non-speech lip movements (global motor difference). Furthermore, the amplitude and duration of speech movements in PWS did not clearly map onto greater variability or a weaker speech motor skill profile.

Many of the studies reviewed had small sample sizes (fewer than 10 PWS) and a large number of measured variables. In addition, the variance within the stuttering group was often high. The combination of these factors limits the power to detect differences between groups and makes finding spurious results more likely. Larger sample sizes will be required to ensure adequate power to detect differences between groups. Large sample sizes may also give adequate power to

understand the individual differences in the stuttering groups and determine whether subtypes of stuttering exist.

3.5.1 Future directions

The methods examined in this review offer new insights into the speech motor control of both typical and dysfluent speech production. Current techniques involve considerable effort to limit disruption of speech movements; nevertheless, each entails alterations to sensory sensations (e.g. by placing electrodes on the skin). This may be particularly important considering theories that predict altered sensory-motor feedback processes in PWS and the known fluency-enhancing effects of altered sensory feedback.

The methods reviewed here are limited to measuring one or two articulators at a time. Speech requires the co-ordinated of control of many articulators. As such, these methods are unable to fully represent the speech motor control of PWS. Recent advances in MRI offer the opportunity to view the movement of the entire vocal tract, without disturbing speech movements, at good temporal and spatial resolution (Carey & McGettigan, 2017; Niebergall et al., 2013; Ramanarayanan, Goldstein, Byrd, & Narayanan, 2013). This allows for measures of the range of movements within different articulators, variability of such movements over repeated utterances, and co-ordination between articulators during speech (Kim, Kumar, Sunbok & Narayanan, 2014). An exciting next step is to measure the speech motor control of PWS using vocal tract imaging.

4 Measuring speech movements in people who stutter using MRI of the vocal tract.

4.1 Abstract

Introduction: The speech motor systems of people who stutter (PWS) are less stable than those of typically fluent controls. Previous measures of lip aperture over repeated utterances of nonwords reported greater variability in PWS than controls (Smith et al., 2010); variability increased with the length and phonological complexity of the nonword in PWS. Here, we examined these effects in PWS using a novel technique of real-time MRI of the vocal tract during speech.

Method: Mid-sagittal images of the vocal tract from lips to larynx were reconstructed at 33.3 frames per second. Data from 28 adults with moderate to severe stuttering and 20 people who are typically fluent (PWTF) were compared. Participants repeated nonwords at their normal speaking rate during scanning. Stimuli were identical to those used by Smith et al (2010); four nonwords of increasing length from 1-3 syllables and two 4-syllable nonwords with contrasting phonological complexity. The imaging data were analysed using a custom Matlab toolbox that uses air-tissue boundary segmentation to track precise movements within the vocal tract (Kim et al., 2014). Lip, tongue body, and velum movements were measured during utterances of the

nonwords. Variability of movement across repeated utterances was calculated using the coefficient of variation. The duration of movements was also compared.

Results: The group of PWS repeated the nonwords with greater variability compared with the group of typically fluent speakers for each of the articulators measured: the lip, the tongue and the velum. There was a significant relationship between variability and syllable length of the nonwords. Lip and tongue movements were more variable than velum movements but variability was strongly correlated between all articulators. Stuttering severity was not related to amount of movement variability in any of the articulators measured. In addition, some PWS made slower utterances than PWTF but only when the nonwords became more complex.

Conclusions: Using real-time MRI of the vocal tract, we found that PWS, on average, produced more variable movements than typically fluent speakers even during fluent productions of simple nonwords. This indicates general, trait-level differences in the control of the articulators between PWS and people who are typically fluent.

4.2 Introduction

The systematic review presented in chapter three summarised key differences between people who stutter (PWS) and people who are typically fluent (PWTF) in the way that the structures within the vocal tract (articulators, e.g. lips, tongue) move to produce speech. These kinematic differences were described even when speech was perceptually fluent. However, previous studies were limited in their ability to capture such a complex system of co-ordinated movements, due to the speed of speech movements and the difficulty of attaching recording equipment (such as electrodes) to articulators within the vocal tract. Here, we aimed to measure articulator movement in PWS and PWTF using a novel, non-invasive technique: real-time magnetic resonance imaging of the vocal tract (vtMRI).

In the systematic review, we concluded that the most consistent evidence for kinematic differences between PWS and PWTF was the variability of speech movements over repeated utterances. Fine-tuned control of the articulators should typically be associated with a low amount of variability across utterances. In contrast, reduced co-ordinated control of the articulatory system would result in large amounts of variability. Measuring variability during fluent productions in PWS tells us whether there are general (trait-level) differences in speech motor control, beyond stuttered moments (state-level).

Variability of lip movements over repeated utterances of nonwords was found to be greater in PWS than PWTF (Smith et al., 2010). Infra-red light-emitting diodes (IREDs) placed on the

upper and lower lips, were used to dynamically measure lip aperture during fluent utterances. Lip movements were tracked during the production of nonwords embedded in a carrier phrase "Bob says ..... again". Three of the nonwords increased in length from 1-3 syllables. Two nonwords had 4-syllables but contrasting phonological complexity. The variability of lip movements was calculated using a Spatio-Temporal Index (STI): a higher STI indicates greater variability over repeated utterances (Smith et al., 1995, 2010). Compared with PWTF, PWS showed greater variability as articulatory complexity was increased by increasing the number of syllables. Lip movement variability was also more pronounced for the phonologically complex four-syllable nonword compared to the simple one.

The findings of the previous study (Smith et al., 2010) are consistent with the hypothesis that speech motor control systems of PWS are affected by the cognitive and motor demands of the target utterance (Namasivayam & Van Lieshout, 2011; Smith et al., 2010). These demands include increasing the length, (Peters et al., 2000), speech rate (Namasivayam et al., 2008), phonological (Smith et al., 2010; Soderberg, 1966) and syntactic (Kleinow & Smith, 2000) complexity of the utterance. Accordingly, complex utterances are more likely to result in stuttered moments compared with simple utterances in children (Gaines, Runyan, & Meyers, 1991; Richels, Buhr, Conture, & Ntourou, 2010) and adults who stutter (Robb, Sargent, & O'Beirne, 2009). Similarly, the EXPLAN hypothesis (Howell & Au-Yeung, 2002) predicts that stuttering moments are more likely to occur during complex utterances due to the increased demands for the planning of speech.

The studies reviewed in chapter three focussed on the movement of a limited number of articulators. It is not known whether internal articulators, such as the velum, also move with greater variability during speech in PWS compared with PWTF. Techniques that were commonly used in the previous work were limited to measuring articulators to which electrodes or sensors could be safely attached; e.g. the lips, jaw and tongue. Vocal-tract MRI is a relatively new technique that offers the opportunity to view the movement of the entire vocal tract at good temporal and spatial resolution (Carey & McGettigan, 2017; J. Kim et al., 2014; Niebergall et al., 2013; Ramanarayanan et al., 2013). A single image of the midline of the vocal tract (mid-sagittal slice) can be recorded in real time, producing 2D video data that captures the fast movement of the all the articulators simultaneously during speech. Of particular interest, movement of articulators that are difficult to attach electrodes to can also be assessed, such as the velum and larynx.

Here, we aimed first to replicate the results of Smith et al., (2010) by measuring lip aperture variability in PWS and PWTF during fluent repetitions of nonwords using vtMRI. Positive replication would serve to validate vtMRI as a method for studying variability in speech motor control. Secondly, we aimed to extend this work to exploit the main benefit of vocal tract imaging: capturing information from multiple articulators simultaneously and non-invasively. In order to focus our analyses, measures were taken from three articulators along the length of the vocal tract: the lips, tongue body, and velum. In addition, we included a large sample of participants who stutter than seen in previous studies and there was a greater range of stuttering severities. This allowed investigation into the relationship between stuttering severity and speech motor control.

4.3 Method

4.3.1 Participants

We scanned 31 adults who stutter and 20 typically fluent, matched controls. One PWS was excluded due to technical reasons. Data from a further two PWS were excluded because fewer than six out of ten utterances were produced fluently during the scan (see analysis plan, below). This resulted in a sample of 28 adults who stutter (seven females, mean age = 30.57 years; range = 19-45) and 20 controls (four females, mean age = 29.4 years; range = 20-44). Groups were matched on sex, age, ethnicity and years of education. All PWS had at least mild stuttering severity, as assessed by the Stuttering Severity Instrument (SSI-4; mean SSI score = 27.37, range = 19-43). Participants had normal or corrected-to-normal vision and normal hearing. Participants had no family history of epilepsy and were not pregnant. Exclusion criteria included any disorder of speech, language or communication other than developmental stuttering.

Participants' speech was assessed using the Stuttering Severity Instrument (SSI-4; (Riley, 2009)). This instrument measures the frequency and duration of stuttered moments as well as physical concomitants. Participants were recorded with video reading a passage and having a conversation with the researcher for two minutes, each. Recordings were scored offline.

All PWS reported the onset of stuttering before 10 years old. 18 participants had received speech and language therapy (median duration = 1.1 years; range = 2 months – 14 years). No participants had received therapy within the last 6 months.

4.3.2 Experimental procedure

Prior to scanning, participants were shown the set of nonword stimuli and asked to read them aloud until they could be produced accurately. This was typically achieved after three repetitions of the nonword set.

The nonword stimuli were identical to those used by Smith et al (2010); four nonwords of increasing length from 1-3 syllables and two 4-syllable nonwords with contrasting phonological complexity. Nonwords started with a bilabial sound. This was crucial for the analysis of lip aperture, previously reported (Smith et al., 2010). In contrast to the previous work nonwords were read in isolation, without a carrier phase.

Table 4.1 Nonword Stimuli.

Syllables	Nonword	IPA
1	"mab"	/mæb/
2	"mabshibe"	/mæbʃaIb/
3	"mabfieshabe"	/mæbfaIʃeIb/
4c	"mabshaytiedoib"	/mæbʃeitaIdɔIb/
4s	"mabteebeebee"	/mæbtibibi/

IPA = International Phonetic Alphabet 4c = complex, 4s = simple

During scanning, each nonword was read 10 times, in a random order. For each trial, the nonword was displayed on a screen and participants read it aloud at their natural speaking rate. Each trial lasted 3.5 seconds. In total, there were 50 trials resulting in a total run time of ~3 minutes.

4.3.3 MRI acquisition

Mid-sagittal images of the vocal tract from lips to larynx were acquired with in-plane spatial resolution of 2 mm x 2 mm using a radial FLASH sequence (TE/TR = 1.4/2.5ms) with golden angle sampling. Images were reconstructed at 33.3 frames per second using a second order spatio-temporal total generalized variation constraint (Knoll et al., 2010). The scan sequence and reconstruction algorithm were custom made by Dr. Mark Chiew at the Oxford centre for Functional MRI of the Brain (FMRIB).

4.3.4 Analysis procedure

The imaging data were reconstructed into a video format and analysed using a custom Matlab toolbox that uses grid-based, air-tissue boundary segmentation to track movements within the vocal tract (Kim et al., 2014). The schematic, below, shows the analysis pipeline (Figure 4.1).

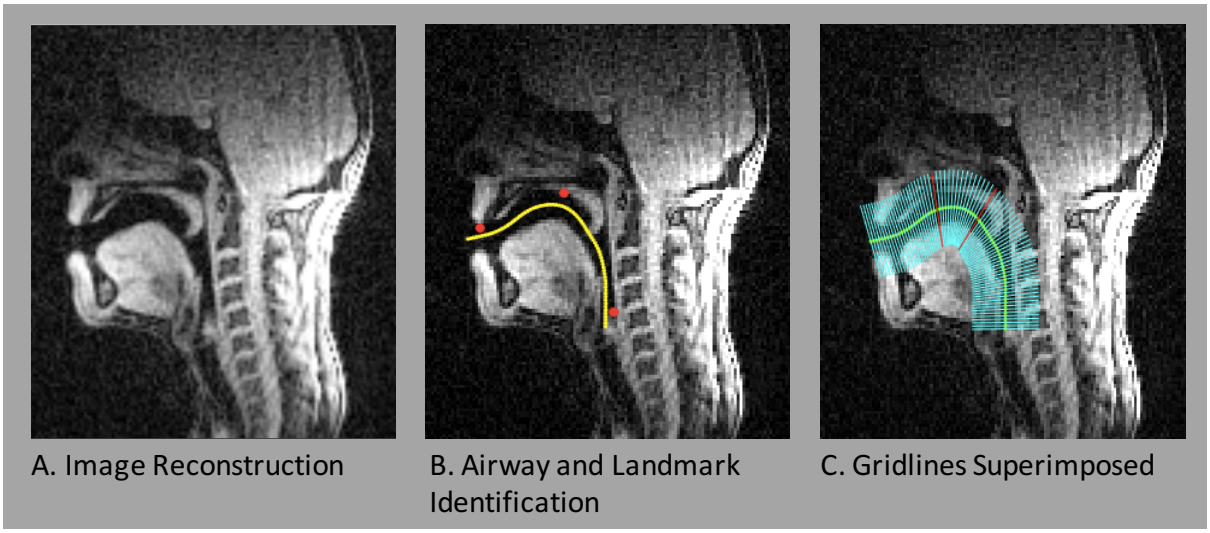


Figure 4.1 Image analysis pipeline.

A: Example (single frame) of the reconstructed image (Chiew et al., in preparation). B: Using the air-tissue boundary toolbox (Kim et al., 2014), the airway was identified manually by drawing a line through the open vocal tract (yellow line). The lowest point of the upper lip, back of the hard palate and larynx were also identified manually (red dots). C: Grid lines were created based on the information shown in B. Equally spaced gridline were placed orthogonal to the yellow line and centred on it. Red gridlines are the ones used for tracking the tongue body (left) and velum (right).

Using the air-tissue boundary toolbox (Kim et al., 2014), the airway was identified manually by drawing a line through the open vocal tract (See yellow line, Figure 4.1 B). The lowest point of the upper lip, back of the hard palate and larynx were also identified manually. These points were used to guide where a grid is placed. Equally spaced gridlines were placed orthogonal to the yellow line and centred on it (Figure 4.1 C). The upper and lower air-tissue boundaries were then identified based on the where abrupt changed in pixel intensity (where white pixels, tissue, meet black pixels, air) intersected with each gridline. The data from each gridline was interpolated and smoothed to create a continuous boundary line. The upper and lower boundaries determined in this way are shown in Figure 4.2, below.

4.3.5 Lip aperture measurement

Lip aperture (the distance between the upper and lower lips in mm) was measured as the distance between the first point of the upper and lower air-tissue boundary (see Figure 4.2).

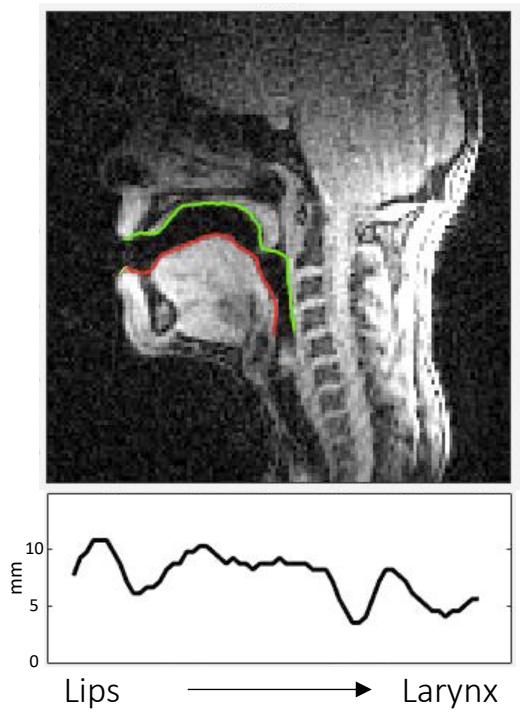


Figure 4.2 Example (single frame) showing tracking of air-tissue boundaries.

Upper airway shown in green. Lower airway shown in red. Lower panel shows difference (in mm) between upper and lower boundary from the lips to the larynx. Lip aperture is measured by extracting the first point from this measurement.

The start of the utterance was identified as the latest time frame at which the lip aperture was zero for the /m/ sound. The end of the utterance was identified as the time frame that the lip aperture first returned to zero for the final bilabial closure of the word, e.g. /b/. An example of the lip aperture traces is shown in Figure 4.3, below.

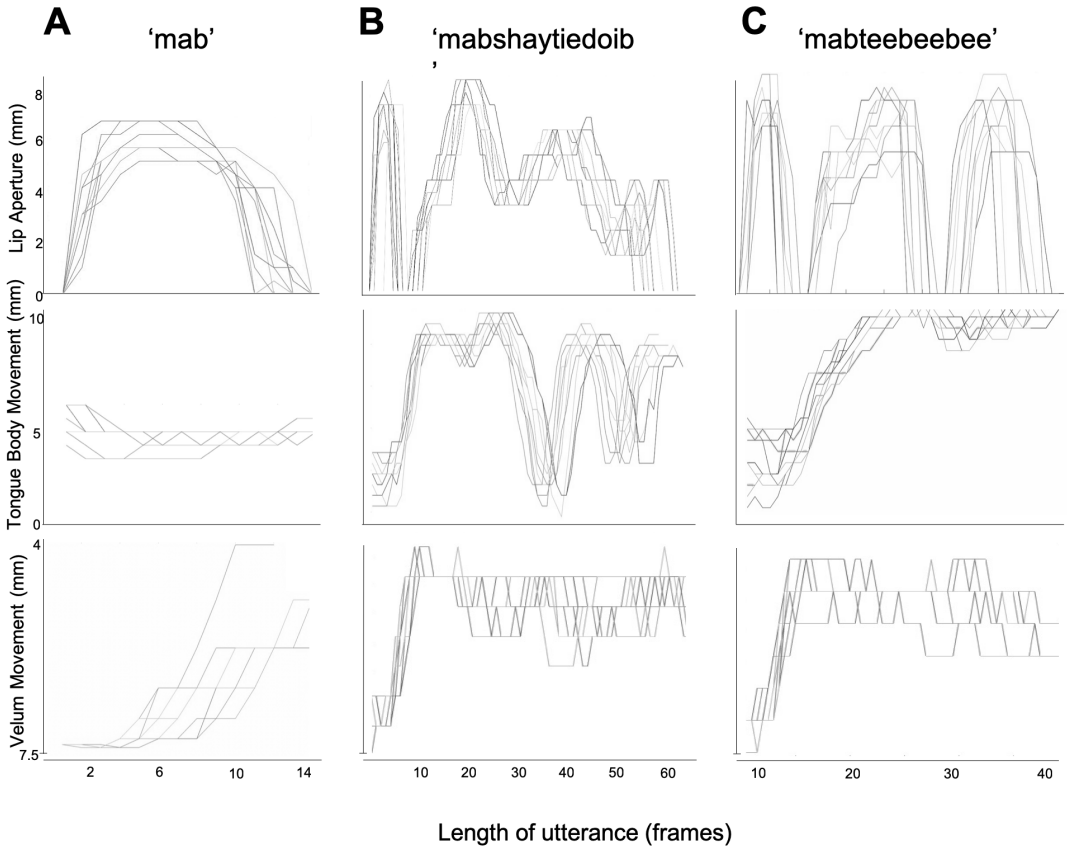


Figure 4.3 Examples of Movement Traces.

Each plot shows 10 repetitions of the words (A) 'mab' and (B) 'mabshaytiedoib' and (C) 'mabteebeebee' for a single participant. Each line represents one repetition. The start and end points are defined as the frame where lip aperture departs from and returns to zero, respectively.

Variability was calculated using the coefficient of variation; that is, the standard deviation of the size of the movements across the 10 repetitions of each word was divided by the mean. The size was simply the sum of the aperture of the movements across frames capturing both the amplitude and duration of the movement.

4.3.6 Velum and tongue body measurements

Velum and tongue movement were measured in a similar way. For tongue body, the position of the lower air tissue boundary (shown in red, Figure 4.2) was tracked as it moved along a single gridline. We selected the gridline that was closest to the highest point of the tongue body in the frame where the tongue reaches its most dorsal extent during the first /e/ sound of 'mabteebeebee'. The lowest point of the tongue from the entire scan was selected as an anchor point to which all frames were compared to. For each frame, the Euclidian distance from this point to the tongue position in that frame was measured. This was done to ensure that all values were positive.

For the velum, the upper air-tissue boundary (shown in green, Figure 4.2) was tracked up and down the velum gridline. This gridline was chosen as the closest gridline to the middle of the velum, which captures the bend in the velum when open, and thus largest range of velum movement. The point at which the velum was highest from the entire scan was selected as an anchor point to which all other frames were compared to.

For the tongue body and the velum, the start and end of the utterance were taken from the lip closure procedure describe above. Therefore, each of the articulators captured the same frames for each utterance. Examples of the tongue body and velum movement are shown in Figure 4.3.

The coefficient of variation for tongue and velum movements was determined as for the lip aperture.

4.3.7 Analysis plan

Errors made during the task, such as pronouncing the nonword incorrectly or stuttering during production of the nonword were rare. Data were excluded for two reasons. Firstly, if a participant did not produce at least six (out of ten) fluent and accurate productions of a nonword, data for that nonword were excluded from analyses. Two full data sets (PWS) were excluded prior to analysis based on this criterion. In total, 8 out of 140 possible nonwords (5.7%) from the stuttering group and four out of a possible 100 nonwords (4%) from the control group were excluded (see Figure 4.7). Secondly, individual utterances were excluded but the nonword included if there were between six and ten valid utterances. The percentages of utterances that were excluded based on this six out of ten criteria are shown in table 4.2.

Table 4.2 Percentage of missing utterances by group and nonword. Raw data shows number of missing utterances out of the total number included in the analysis after whole nonwords (all 10 utterances) were excluded.

Nonword	PWS	PWTF
1	2.20 % (6/270)	2.10 % (4/190)
2	2.60 % (7/260)	1.00 % (2/200)
3	8.40 % (21/250)	4.20 % (8/190)
4 (complex)	3.85 % (10/260)	5.00 % (9/180)
4 (simple)	2.96 % (8/270)	1.5 % (3/200)

All statistical analyses were completed in R (R Core Team, 2019). Linear mixed models were used because we could model complex interactions between group, word and articulator levels and because they can account for the fact that multiple responses from the same person are more similar than responses from other people by including subject as a random factor. In addition, linear mixed models are robust to a small amount of random missing data, allowing us to use all available data (Krueger & Tian, 2004). Linear mixed models were calculated using the lme4 package in R (Bates, Mächler, Bolker, & Walker, 2015).

Four linear mixed models were used to capture: 1) variability in relation to word length (words 1 to 3); 2) variability in relation to phonological complexity (words 4c and 4s); 3) duration (words 1 to 3); and 4) duration in relation to phonological complexity (words 4c and 4s). All models included participant as random factor. For models measuring variability (models 1 and 2), word length was nested as a random factor with participant to account for variability of word within participants.

Main effects and interactions are reported using the 'anova' command from stats package (R Core Team, 2019) with Type III Analysis of Variance with Satterthwaite's method (Luke, 2017). Full models (with comparisons between each factor for categorical variables) are shown in Tables 4.6 – 4.9 at the end of this chapter. Marginal and conditional R^2 were calculated to represent the variability accounted for by the fixed effects alone and the fixed and random effects in the model, respectively. Normalized beta estimates were calculated using the *stdbeta* function of the *sjstats* package in R to facilitate comparison of effect size across the independent variables within each model.

4.4 Results

4.4.1 Are there differences between the variability of speech movements of PWS and PWTF? Does nonword length affect variability?

The amount of variability for each word and group is plotted for each articulator in turn in Figures 4.4-4.6. The pattern of results across all articulators for each individual participant is shown in Figure 4.7.

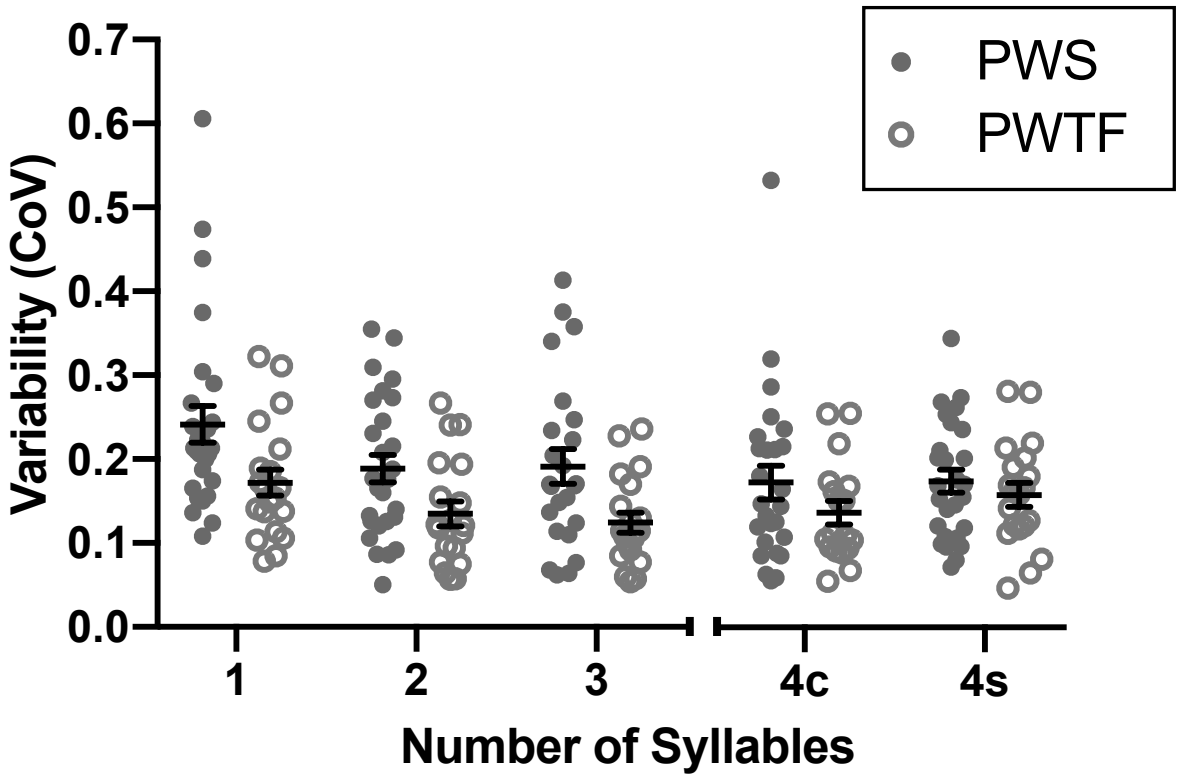


Figure 4.4 Variability of lip aperture over repeated utterances of the 'mab' nonword set.

CoV = coefficient of variation. PWS = People who stutter, PWTF = People who are typically fluent. 4c = 4-syllable, complex word ('mabshaytiedoib'), 4s = 4-syllable, simple word ('mabteebeebee'). Horizontal

lines represent the mean and error bars show standard error of the mean. Individual participants are represented by each circle. Filled circles = PWS; open circles = PWTF.

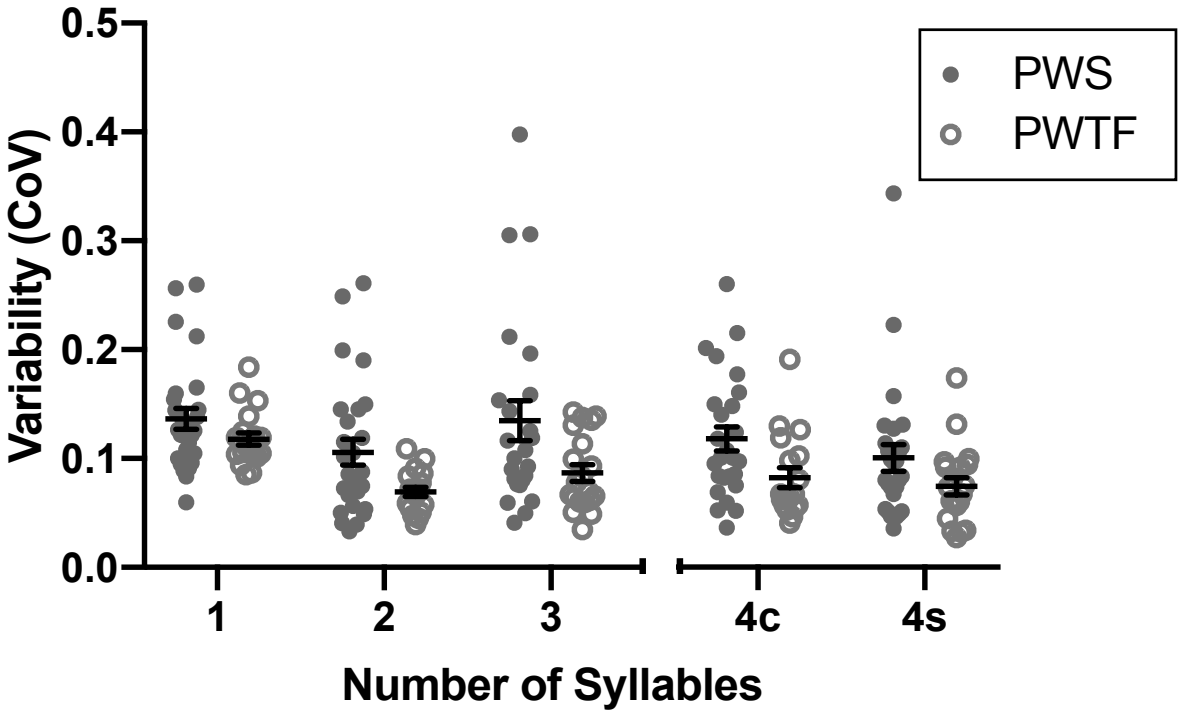


Figure 4.5 Variability of velum movements over repeated utterances of the 'mab' nonword set.

See legend to Figure 4.4 for details.

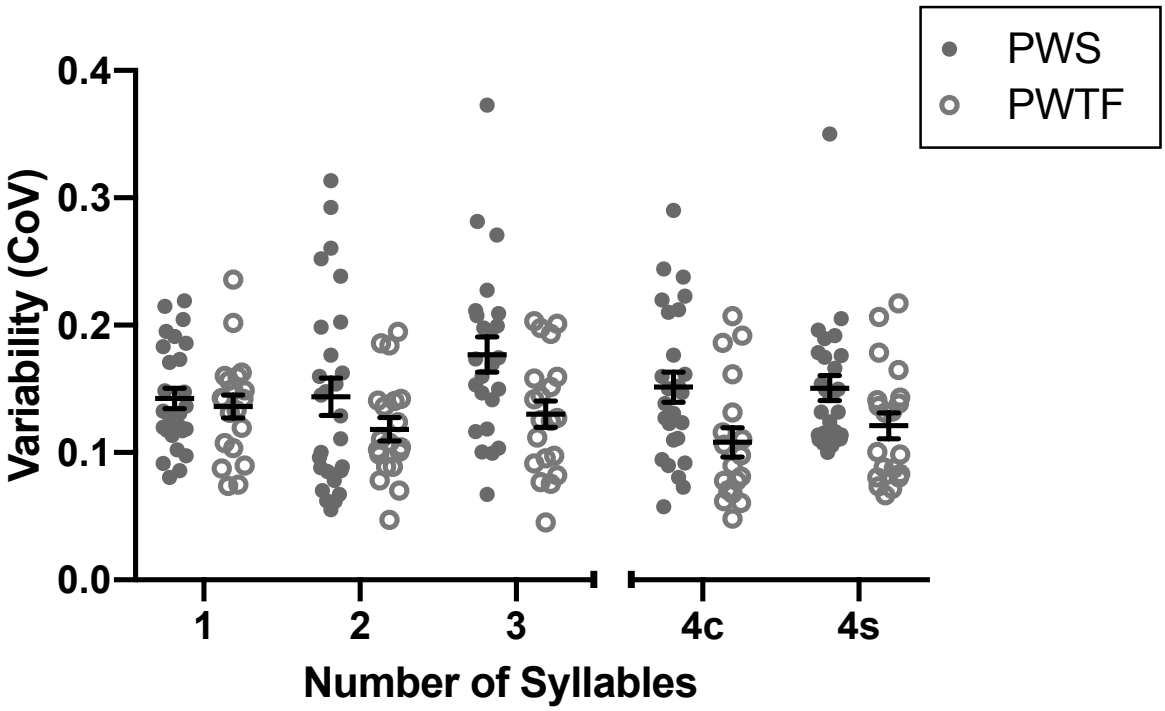


Figure 4.6 Variability of tongue body movements over repeated utterances of the 'mab' nonword set.

See legend to Figure 4.4 for details.

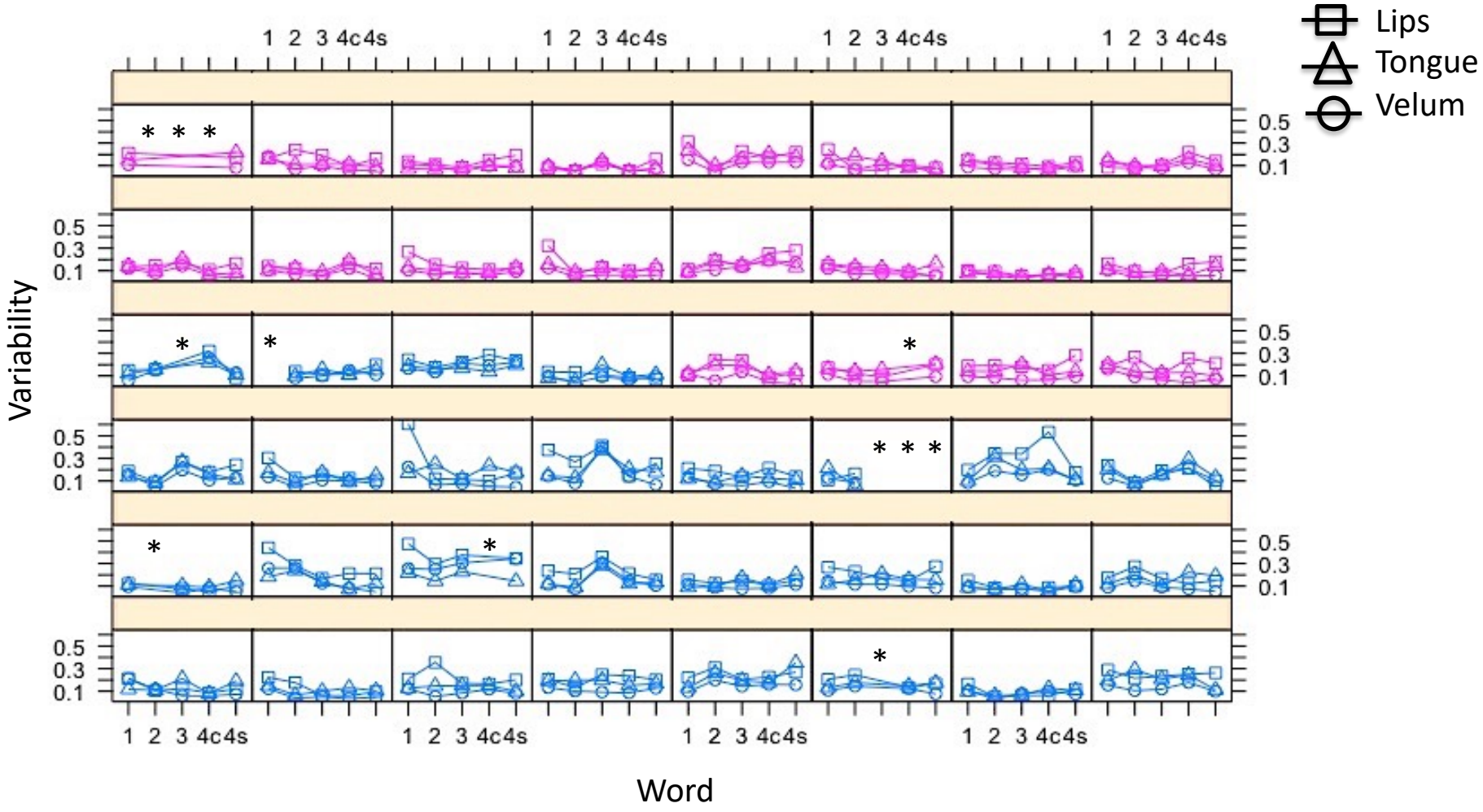


Figure 4.7 Individual variability scores for words with 1-3 syllables and the complex (4c) and simple (4s) 4-syllable nonwords.

Pink participants = PWTF, Blue participants = PWS. Data from some participants are missing due to speech errors (such as mispronouncing the word or stuttering). * represents missing data.

The overall model predicting variability (formula = variability ~ group * word(1 to 3 syllables) * articulator + (1 + word | p_code), REML = TRUE, contrasts = contra.sum) had a total explanatory power (conditional R^2) of 69.79%, in which the fixed effects explain 26.05% of the variance (marginal R^2). Main effects and interactions are displayed in Table 4.3. Within this model the main effects of group, word and articulator were significant. In addition there was a significant interaction between group and articulator as well as between word and articulator. These interactions were explored using the full model results, which are displayed in Table 4.7.

Table 4.3 The effect of word length on variability.

	df	Den df	F	*p*
Group	1	45.954	10.466	**0.002**
Word	2	44.039	5.327	**0.008**
Articulator	2	261.997	81.402	**<0.001**
Group x Word	2	44.039	0.505	0.607
Group x Articulator	2	261.997	6.051	**0.003**
Word x Articulator	4	261.997	6.602	**<0.001**
Group x Word x Articulator	4	261.997	1.187	0.317

Type III Analysis of Variance Table with Satterthwaite's method

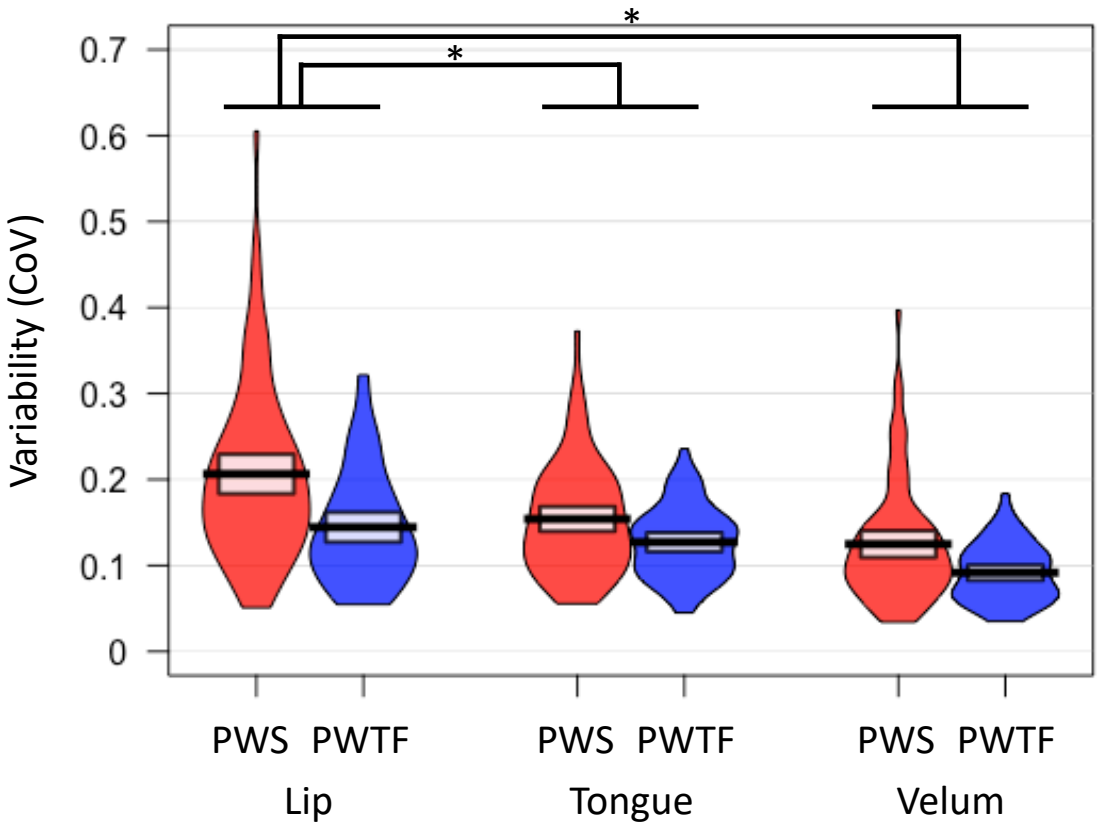


Figure 4.8 Graph showing violin plots of the main effects and interactions of group and articulator collapsed over words of 1-3 syllables.

PWS = red, PWTF = blue. Horizontal line shows means, boxes show confidence interval. Coloured areas indicate the data distribution. Significant interactions between group and articulator are shown with an asterisk.

The model indicates that overall, PWS were significantly different to PWTF (significant effect of Group; Table 4.3) and examination of the means indicates that PWS had greater variability than PWTF (see Figure 4.9). There was a larger group difference for lip compared with tongue and velum movements but not between tongue and velum movements (significant interaction between group and articulator; see Table 4.3; Figure 4.8). The main effect of word was driven by significantly higher variability when repeating the one-syllable word compared to the two-

syllable *(p < .001)* and three-syllable word (*p < .002*), which did not differ. The main effect of articulator was explained by higher variability for the lip than for the tongue (*p < .001*) and velum (*p < .001*) movements, which did not differ. Finally, there was a significant interaction between word and articulator that was driven by bigger decreases in variability from one- to three-syllable words for lip compared with velum (*p = .003)* and tongue movements (*p < .001)*.

4.4.2 Does phonological complexity of the word affect variability?

The overall model predicting variability (formula = variability ~ group * word * articulator + (1 + word | p_code), REML= TRUE, contrasts = contra.sum) has a total explanatory power (conditional R^2) of 58.72%, in which the fixed effects explain 20.98% of the variance (marginal R^2). Within this model the main effect of group was significant. In addition, there was a main effect of articulator but there were no significant interactions. Full results for this model are displayed in table 4.4, below.

Table 4.4 The effect of phonological complexity on variability

	df	Den df	F	*p*
Group	1	39.511	6.078	**0.018**
Word	1	40.379	0.017	0.896
Articulator	2	174.002	48.713	**<0.001**
Group * Word	1	40.379	0.757	0.389
Group * Articulator	2	174.002	0.284	0.753
Word * Articulator	2	174.002	1.766	0.174
Group * Word x Articulator	2	174.002	0.072	0.930

Type III Analysis of Variance Table with Satterthwaite's method

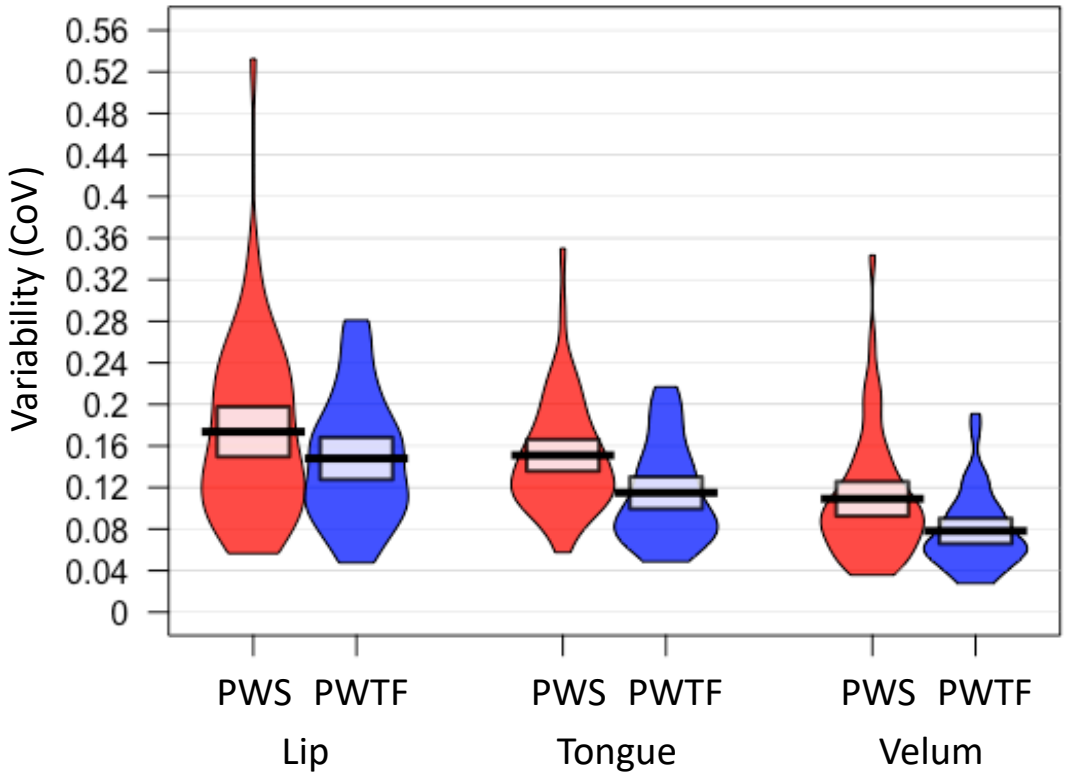


Figure 4.9 Graph showing violin plots of group and articulator collapsed over the two, 4-syllable nonwords.

PWS = red, PWTF = blue. Horizontal line shows means, boxes show confidence interval. Coloured areas indicate the data distribution.

The full model shows that PWS had greater variability than controls. The main effect of articulator was explained by both lip ($p<.001$) and tongue variability ($p = .008$) being significantly greater than velum variability (no interaction).

4.4.3 Is there a relationship between the variability of the articulators?

The above models suggest that there is a difference in the amount of variability depending on the articulator. It is also of interest to test whether these differences are still related, i.e. if a large amount of variability for lip is associated with a large amount of variability for the tongue etc.

For these analyses the four syllable complex word ('mabshaytiedoib') was used as this we predicted that this word would result in the greatest variability.

The amount of variability over repetitions of 'mabshaytiedoib' (4c) for each articulator were strongly correlated for PWS (lip vs. velum: r = .806, $p < .001$; lip vs. tongue: r = .699, $p < .001$; velum vs. tongue: r = .842, $p < .001$) and PWTF (lip vs. velum: r = .778, $p < .001$; lip vs. tongue: r = .760, $p < .001$; velum vs. tongue: r = .690, $p < .001$). There was no difference between groups for each of the correlations (lip vs. velum: $Z = 0.40$, $p = .409$; lip vs. tongue: $Z = -0.40$, $p = .344$, velum vs. tongue: $Z = 1.17$, $p = .122$).

4.4.4 Is there a relationship between stuttering severity and speech motor control (PWS only)?

The relationship between lip movement variability data for 'mabshaytiedoib' (4c) and SSI score is plotted in Figure 4.10, below. There was no correlation between variability score and SSI score (r = -.093, $p = .659$).

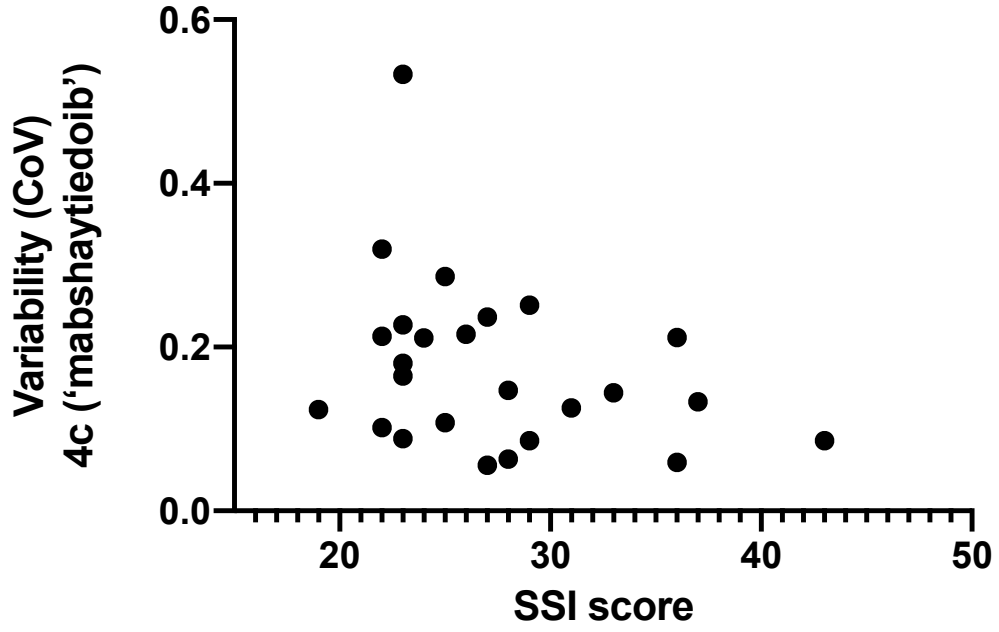


Figure 4.10 No Relationship Between Variability of Articulator Movement and SSI Score.

Each point represents an individual participant who stutters.

4.4.5 Are there differences in the duration of utterances between PWS and PWTF?

The duration of responses for each word and group is plotted in Figure 4.11, below.

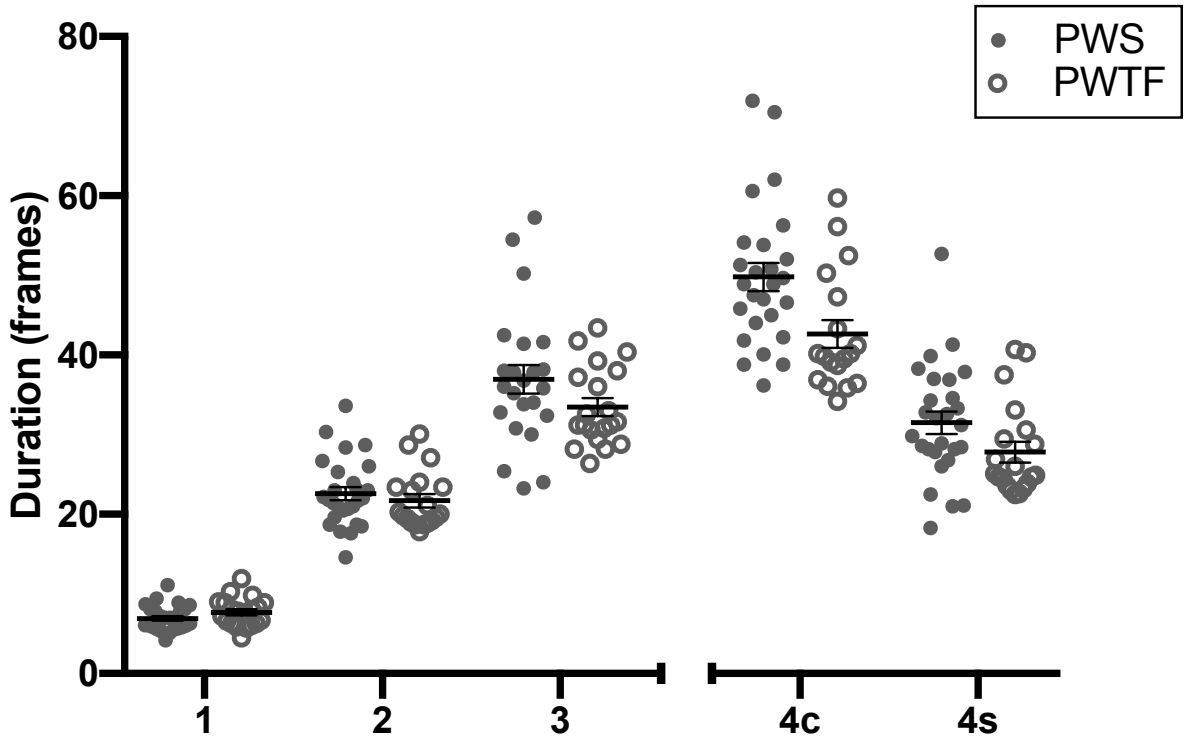


Figure 4.11 Duration of responses.

PWS = people who stutter, PWTF = people who are typically fluent. 4c = 4-syllable, complex word ('mabshaytiedoib'), 4s = 4-syllable, simple word ('mabteebeebee'). Horizontal lines represent mean and error bars show standard error of the mean.

The overall model predicting duration (formula = mean_duration ~ group * word + (1 | p_code), REML = TRUE, contrasts = contr.sum) has a total explanatory power (conditional R^2) of 93.79%, in which the fixed effects explain 85.67% of the variance (marginal R^2). Main effects and interactions between the fixed effects are shown in Table 4.5, below. Within this model, the effects of word (highly expected as words with more syllables would have longer durations) and the interaction between group and word were significant. The main effect of group was not significant. Full results are presented in Table 4.9.

Table 4.5 The effect of nonword length on duration

	df	Den df	F	*p*
Group	1	46.507	1.187	0.282
Word	2	361.836	2618.082	**<0.001**
Group * Word	2	361.836	15.619	**<0.001**

Type III Analysis of Variance Table with Satterthwaite's method

The interaction is due to greater variability in PWS compared with PWTF for the two- and three-syllable nonwords compared with the group difference for the one-syllable nonword (Figure 4.11, Table 4.5).

4.4.6 Does phonological complexity of the word affect duration?

The overall model predicting duration (formula = mean_duration ~ group * word + (1 | p_code)) has a total explanatory power (conditional R^2) of 94.37%, in which the fixed effects explain 56.79% of the variance (marginal R^2). Main effects and interactions between the fixed effects are shown in Table 4.6, below. Within this model, the effect of word was significant, as expected due to the increased time it takes to produce 'mabshaytiedoib' compared with 'mabteebeebee'. Of interest, the effects of group and the interaction between group and word were significant. The directions of these effects are shown in the full model, which suggests that PWS were more affected by phonological complexity than PWTF. The full model is presented in Table 4.10.

Table 4.6 The effect of phonological complexity on duration

	df	DenDF	F	*p*
Group	1	44.848	5.363	**0.025**
Word	1	224.599	2282.295	**<0.001**
Group * word	1	224.599	13.142	**<0.001**

Type III Analysis of Variance Table with Satterthwaite's method

The interaction is due to a larger effect on duration of movements in PWS compared with PWTF when phonological complexity was increased (Table 4.6). In addition, the main effect of group was explained by PWS having overall longer durations for both words than PWTF.

1.1 Discussion

We tested whether there were differences in articulator movements during perceptually fluent speech between people who stutter (PWS) and people who are typically fluent (PWTF). We used a novel method, MRI of the vocal tract (vtMRI), to capture movement of the lips, tongue body and velum of 26 PWS and 20 PWTF as they repeated nonwords. The nonwords were designed to determine the effects of word length (1-3 syllables) and phonological complexity (Smith et al., 2010). We found differences in the variability of articulator movement and duration of responses between PWS and PWTF. Overall, the stuttering group repeated the utterances with more variability than the control group but this effect did not interact with nonword length or phonological complexity. There was a main effect of nonword length that was driven by higher variability scores for the 1-syllable compared to the 2- and 3-syllable nonwords. In addition, there was a main effect of articulator, accounted for by lower variability for velum movements compared with both the lip and tongue movements. There was no relationship between variability score and stuttering severity. We found an interesting interaction between nonword length and duration, such that PWS repeated utterances more slowly than PWTF as nonword length and phonological complexity increased. This work supports previous investigations of speech motor control in PWS showing a greater amount of variability in the fluent speech movements of PWS compared to PWTF (Frisch et al., 2016; Howell et al., 2009; Jackson et al., 2016; Loucks & De Nil, 2006b, 2012; Loucks et al., 2007; Sasisekaran, 2013; Smith et al., 2010). We also extend previous findings by measuring articulators that, until now, have been difficult to capture due to their positioning within the vocal tract. VtMRI is shown to be a useful tool for measuring movements within the vocal tract with good temporal and spatial precision that is

sensitive enough to measure subtle differences in speech motor control between typical and clinical groups.

4.4.7 PWS speak with greater variability than PWTF

The results of the current study reveal a strong effect of group on variability with PWS repeating nonwords with greater variability than controls. However, in contrast to previous findings, we did not find that complexity of the utterance (nonword length or phonological complexity) had an effect on the variability of utterances that is larger for PWS than PWTF (Kleinow & Smith, 2000; Smith et al., 2010; Soderberg, 1966). Instead we found a main effect of nonword length that was driven by higher variability for the shortest word compared to longer nonwords. This is surprising given our hypothesis that the shortest nonword should result in the least amount of variability compared to longer nonwords. Taken together, this suggests that PWS have greater variability than PWTF even during short, simple utterances, possibly more so. It may be that the current study had greater sensitivity to detect differences during short, simple utterances compared to previous work due to the large number of participants (N=26). However, this does not explain why, in the current study, the shortest nonword was repeated with greater variability than the other longer nonwords across both group and articulator. Further replication of this latter effect is warranted before speculation regarding this result.

4.4.8 Differences in analysis procedures

A key difference in this study compared with the previous one (Smith et al., 2010) was the measure used to capture variability of the movements. The previous study used the measure of spatio-temporal index (STI; (Riley, 2009) and here, I used the coefficient of variation (CoV).

The key difference between these methods is that the STI uses normalisation to remove information regarding the amplitude and duration variability in order to determine variability of the relative timing of the articulator movement. In contrast, CoV captures variability in amplitude and duration, and normalises for the increased length of the word (as the standard deviation, is divided by the mean of the utterance). This enables direct comparison of variability between nonwords of different lengths. In our opinion, these differences are unlikely to explain the subtle differences in results between the two studies.

4.4.9 Capturing variability in multiple articulators

In addition to measuring the lip aperture, we aimed to measure the movement of articulators that were previously difficult to measure non-invasively due to their positioning within the vocal tract (tongue and velum). This exploits the benefits of vtMRI. In addition to the lip aperture, we also measured variability for the tongue body and the velum. There was a strong correlation between the amount of variability for each of the articulators, but overall, there was less variability for velum movements compared with both lip and tongue movements. This effect of articulator may be due to the different involvement of the articulators in each of the utterances. The nonwords were taken from a previous study and were designed to contain bi-labial sounds (lip closures) in order to capture the movements of the lips. The lack of nasals in this specific nonword set reduced the amount of velum movement required to produce the utterances. Figure 4.8 demonstrates that the velum movement is less variable compared with the lip and tongue movements. Overall our results suggest that variability generalises across articulators (e.g. if participants had high variability for the lips, they were likely to have high variability for the velum and tongue as well).

4.4.10 Variance within the stuttering group

Importantly, many PWS have levels of variability that are within the range of PWTF. This means that increased variability cannot be considered a diagnostic characteristic of developmental stuttering. Instead, there could be subtypes within PWS whereby reduced control over the articulators is characteristic of a subset of PWS, only. Interestingly, these potential subgroups are not explained by severity of stuttering, as there was no relationship between severity (SSI) and variability (Figure 4.10). When considering the implications of these results for theory and the clinic, it is important to bear in mind that not all PWS have increased variability compared with PWTF.

4.4.11 What does variability represent?

Variability is thought to represent a general measure of speech motor control, in which random noise is inserted into the motor plan at some stage prior to execution. It is thought that this noise comes from altered communication within the nervous system; from planning to execution of speech. For example, reduced connectivity between sensory and motor regions of the brain in PWS compared with PWTF may introduce noise at the neural level (Connally et al., 2014; Neef et al., 2015, 2011; Watkins et al., 2008). However, it is clear that this noise cannot be pinned to one specific process within the nervous system using measures of kinematic variability. In addition, this noise may also be caused by cognitive or social factors. Variability, as measured here, can tell us about general differences in the control of speech movements between PWS and PWTF but cannot show where this variability comes from.

4.4.12 Implications of greater variability in PWS compared with PWTF.

As well as there being ambiguity about the source of variability, it is unclear whether greater variability has further implications for stuttering. Figure 4.12 demonstrates three possible predictions based on hypotheses that predict differences in the feedforward and feedback control of speech (Bohland et al., 2010; Guenther, 2016; Hickok, Houde, & Rong, 2011; Max et al., 2004). According to these models, stuttering is caused by a discrepancy between the expected utterance (sensory and auditory predictions) and the actual utterance produced. An error signal may be produced in three ways; 1) the predictive space is faulty, causing a noisy error signal which prompts the movements to constantly adapt to try to 'fix' the discrepancy, thus causing increased variability (Hickok et al., 2011; Max et al., 2004) (Fig 4.12 B); 2) the predictive space is typical, but the more variable movements fall outside of this range (Fig. 4.12 C); or 3) the movements have a typical amount of variability but the prediction space is smaller, resulting in less tolerance of typical movement variability (Fig. 4.12 D). Our data (in accordance with the findings from the systematic review, chapter 3) support the predictions 1 and 2: that PWS have more variability in their speech because the sensory-motor feedback (what actually happened) will not match with a predicted response (what the brain thought would happen). This would result in an error signal. The error signal generated may result in an inhibitory response, resulting in a block, repetition or prolongation of the sound. However, our data cannot distinguish as to whether a noisy error signal causes variability (prediction 1) or variability causes the error signal (prediction 2).

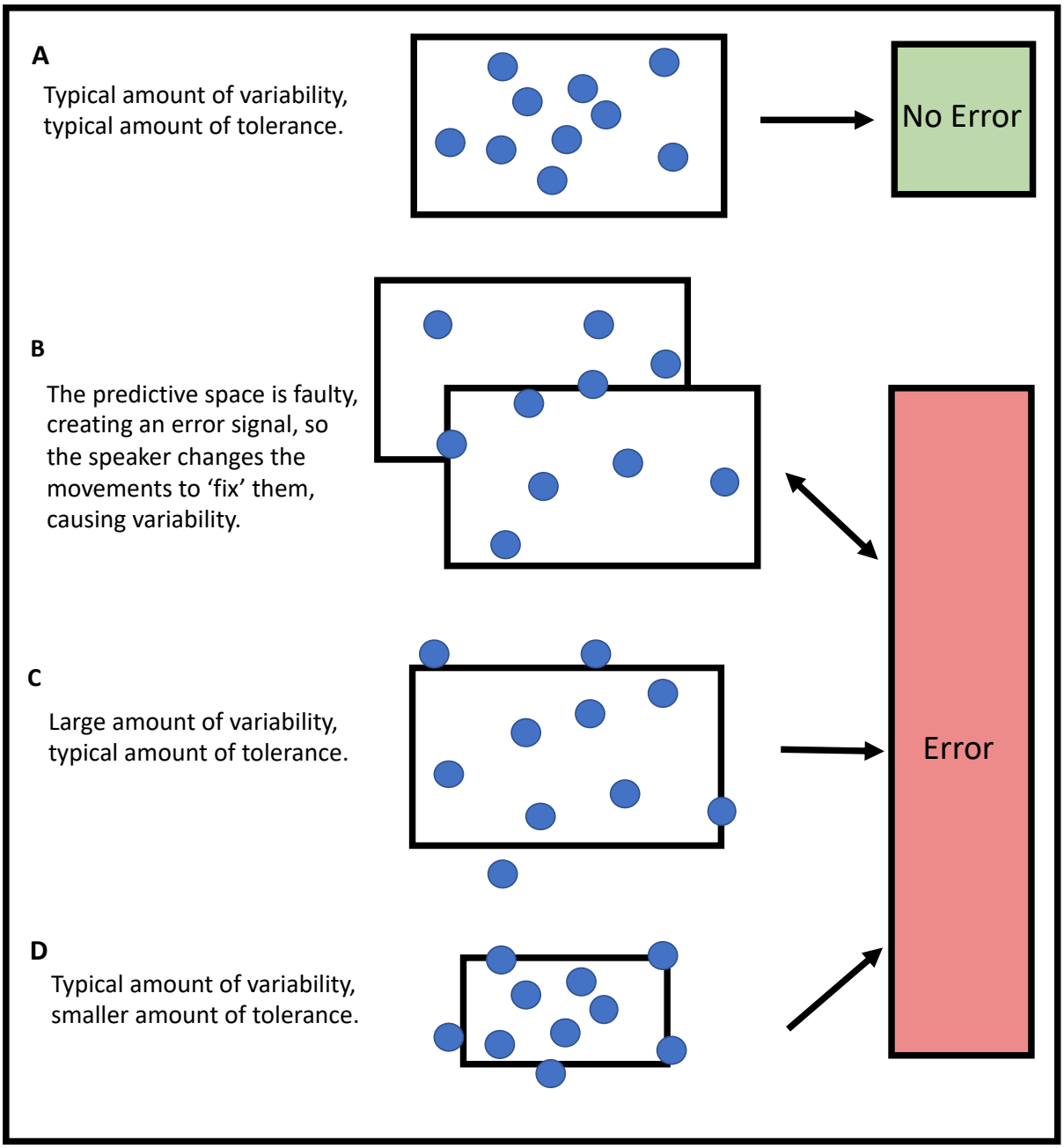


Figure 4.12 Possible explanation for the role of variability in speech motor control.

A) The actual movement (blue dots) fall within the predicted range (black square) resulting in no error signal. B) The error signal is noisy, causing the speaker to attempt to "fix" movements that may have been correct. Attempting to update plans for every utterance using this noisy error signal results in increased motor variability; that is, each new utterance is "updated" with faulty errors, leading to overall variability across utterances C) The actual movements are more variable and therefore sometimes fall outside of the predicted range. D) The predicted range is smaller (less tolerant to variability) and so an error signal is produced even though the movements have typical variability. Our data support predictions B and C.

Our data suggest that there is no simple linear relationship between the amount of variability and stuttering severity. This may be explained by the fact that SSI measures a range of characteristics of stuttering, including duration of stuttered moments and physical concomitants. In addition, stuttering severity is known to be affected by factors beyond speech motor control, such as learned anxiety in response to stuttering (Alm, 2014). The relationship between variability and severity may be further complicated by compensation strategies. For example, PWS may reduce their speech rate in order to maintain fluency (Andrews, Howie, Dozsa, & Guitar, 1982). There is some evidence that increasing speech rate to a faster than typical rate leads to greater variability in PWS (Namasivayam et al., 2008), however, the effect of slowing speech rates on variability in not clear.

Our data show that some PWS made utterances with longer durations than PWTF but only when the nonwords became more complex (either due to more syllables or phonological complexity). As greater demands are placed on the speech motor system, it could be that PWS compensate by slowing down their speech (Max, Caruso, & Gracco, 2003; Peters, Hulstijn, & Starkweather, 1989; Van Lieshout, Hulstijn, & Peters, 1996a). It has also been hypothesised that slowing speech rate would allow accumulation of evidence from feedback (sensory reafference) (Watkins et al., 2016). This may be an automatic response at neural level, or could represent a conscious effort to maintain fluency. Fluency-enhancing techniques such as altering auditory feedback, choral speaking, and singing all typically involve slower production. Speech-language therapies often focus on slowing speech rate in order to improve fluency. The participants in our study received therapy, some of which targeted speech rate. It is therefore plausible that some PWS consciously slow down their speech when the utterance becomes more difficult. Future studies should examine the effect of slowing down speech rate on variability.

In summary, we part-replicated previous findings that show PWS have greater variability in the movements of the articulators during fluent utterances compared with PWTF (Kleinow & Smith, 2000; Smith et al., 2010). In addition, we extended our previous knowledge by exploiting the benefits of vtMRI to measure multiple articulators within the vocal tract. Our results show that vtMRI is sensitive to subtle differences in articulator movement between PWS and PWTF, even during perceptually fluent speech.

4.5 Full Model Outputs

Table 4.7 Effect of word length on variability.

			Variability (CoV)	
Predictors	*std. Beta*	*Estimates*	*CI*	*p*
(Intercept)		0.24	0.22 – 0.26	**<0.001**
Group PWS:PWTF	-0.14	-0.07	-0.11 – -0.03	**<0.001**
Word 1:2	-0.10	-0.05	-0.08 – -0.02	**0.001**
Word 1:3	0.22	-0.05	-0.09 – -0.02	**0.002**
Word 2:3	0.05	0.03	-0.01 – 0.06	0.102
Articulator Lip:Velum	0.09	-0.10	-0.13 – -0.08	**<0.001**
Articulator Lip:Tongue	-0.33	-0.10	-0.12 – -0.08	**<0.001**
Articulator Velum:Tongue	-0.09	0.01	-0.02 – 0.03	0.611
Group PWS:PWTF * word 1:2	0.08	0.02	-0.03 – 0.06	0.490
Group PWS:PWTF * word 1:3	-0.64	0.01	-0.04 – 0.06	0.778
Group PWS:PWTF * word 2:3	0.23	-0.01	-0.06 – 0.04	0.688
Word1:2 * Lip:Velum	0.03	0.02	-0.01 – 0.05	0.181
Word1:3 * Lip:Velum	0.36	0.05	0.02 – 0.08	**0.003**
Word2:3 * Lip:Velum	-0.08	0.03	-0.01 – 0.06	0.098
Word1:2 * Lip:Tongue	-0.09	0.05	0.02 – 0.09	**0.001**
Word1:3 * Lip:Tongue	0.29	0.09	0.06 – 0.12	**<0.001**
Word2:3 * Lip:Tongue	0.11	0.03	0.00 – 0.07	**0.040**
Word1:2 * Velum:Tongue	0.06	0.03	-0.00 – 0.06	0.051
Word1:3 * Velum:Tongue	0.13	0.04	0.01 – 0.07	**0.021**

Word2:3 * Velum:Tongue	0.08	0.01	-0.03 – 0.04	0.691
Group PWS:PWTF * Lip:Velum	-0.33	0.05	0.02 – 0.09	**0.005**
Group PWS:PWTF * Lip:Tongue	-0.44	0.06	0.03 – 0.10	**<0.001**
Group PWS:PWTF * Velum:Tongue	-0.12	0.01	-0.02 – 0.05	0.489
Group PWS:PWTF * Word 1:2 * Lip:Velum	-0.61	-0.03	-0.08 – 0.02	0.189
Group PWS:PWTF * Word 1:3 * Lip:Velum	0.36	-0.03	-0.08 – 0.02	0.179
Group PWS:PWTF * Word 2:3 * Lip:Velum	0.00	0.00	-0.05 – 0.05	0.968
Group PWS:PWTF * Word 1:2 * Lip:Tongue	-0.09	-0.04	-0.09 – 0.01	0.168
Group PWS:PWTF * word 1:3 * Lip:Tongue	0.29	-0.05	-0.10 – -0.00	**0.045**
Group PWS:PWTF * Word 2:3 * Lip:Tongue	0.10	-0.02	-0.07 – 0.03	0.527
Group PWS:PWTF * Word 1:2 * Velum:Tongue	0.64	-0.00	-0.05 – 0.05	0.949
Group PWS:PWTF * Word 1:3 * Velum:Tongue	0.09	-0.02	-0.07 – 0.03	0.509
Group PWS:PWTF * Word 2:3 * Velum:Tongue	-0.04	-0.02	-0.07 – 0.04	0.553

Random Effects

Marginal R^2	0.261
Conditional R^2	0.698
$N_{participant}$	48
Observations	411

R formula = variability ~ group * word(1 to 3 syllables) * articulator + (1 + word | p_code), REML = TRUE, contrasts = contra.sum)

Table 4.8 Effect of phonological complexity on variability.

		Variability (CoV)		
Predictors	*Std. Beta*	*Estimates*	*CI*	*p*
(Intercept)		0.18	0.15 – 0.20	**<0.001**
Group PWS:PWTF	-0.26	-0.04	-0.08 – 0.00	0.077
Word 4c:4s	-0.04	-0.00	-0.03 – 0.03	0.932
Articulator Lip:Velum.	-0.11	-0.05	-0.08 – -0.03	**<0.001**
Articulator Lip:Tongue	-0.15	-0.02	-0.05 – 0.00	0.086
Articulator Velum:Tongue	0.11	0.03	0.01 – 0.06	**0.008**
Group PWS:PWTF * Word 4c:4s	-0.38	0.02	-0.02 – 0.07	0.382
Word 4c:4s * Lip:Velum	-0.01	-0.02	-0.05 – 0.02	0.275
Word 4c:4s * Lip:Tongue	0.00	-0.00	-0.04 – 0.03	0.894
Word 4c:4s * Velum:Tongue	0.00	0.02	-0.02 – 0.05	0.337
Group PWS:PWTF * Lip:Velum	-0.02	0.00	-0.04 – 0.04	0.981
Group PWS:PWTF * Lip:Tongue	-0.01	-0.01	-0.05 – 0.03	0.714
Group PWS:PWTF * word 4c:4s * Lip:Velum	-0.02	-0.01	-0.06 – 0.04	0.706
Group PWS:PWTF * word 4c:4s * Lip:Tongue	0.12	-0.01	-0.06 – 0.05	0.822
Group PWS:PWTF * Word 4c:4s * Velum:Tongue	0.04	0.00	-0.05 – 0.06	0.878
Random Effects				
Marginal R^2		0.210		
Conditional R^2		0.587		
$N_{participant}$		47		
Observations		273		

Table 4.9 Effect of word length on duration

		Mean Duration (frames)		
Predictors	*Std. Beta*	*Estimates*	*CI*	*p*
(Intercept)		6.87	5.46 – 8.29	**<0.001**
Group PWS:PWTF	0.03	0.82	-1.37 – 3.00	0.465
Word 1:2	0.63	15.75	14.83 – 16.67	**<0.001**
Word 1:3	1.12	28.57	27.62 – 29.52	**<0.001**
Word 2:3	0.5	12.82	11.87 – 13.76	**<0.001**
Group PWS:PWTF * Word 1:2	-0.05	-1.74	-3.16 – -0.31	**0.017**
Group PWS:PWTF * Word 1:3	-0.12	-4.10	-5.54 – -2.66	**<0.001**
Group PWS:PWTF * Word 2:3	-0.07	-2.36	-3.81 – -0.92	**0.001**
Random Effects				
Marginal R^2		0.857		
Conditional R^2		0.938		
$N_{participant}$		48		
Observations		411		

Table 4.10 Effect of phonological complexity on duration

		Mean Duration (frames)		
Predictors	*Std. Beta*	*Estimates*	*CI*	*p*
(Intercept)		49.33	46.55 – 52.10	**<0.001**
group PWS:PWTF	-0.26	-6.21	-10.47 – -1.96	**0.004**
Word 4c:4s	-0.77	-17.82	-18.69 – -16.95	**<0.001**
Group PWS:PWTF * word 4c:4s	0.09	2.51	1.15 – 3.87	**<0.001**
Random Effects				
Marginal R^2		0.568 /		
Conditional R^2		0.944		
N_{p_code}		47		
Observations		273		

5 An fMRI study of initiation and inhibition of manual and speech responses in people who stutter

5.1 Abstract

Introduction: Developmental stuttering is a speech motor disorder characterised by difficulties with initiation of speech and frequent interruptions to the speech flow. Previous work suggests that people who stutter (PWS) have an overactive response suppression mechanism (Neef et al., 2018). Accordingly, imaging studies consistently reveal over-activity of the right inferior frontal cortex in PWS (Brown et al., 2005), an area robustly implicated in inhibitory control of both manual and spoken responses (Xue et al., 2008). Here, we employed manual response version of the stop-signal task in fMRI to investigate neural differences related to response initiation and inhibition in PWS.

Method: We analysed behavioural data during a manual stop-signal task in 38 people with moderate to severe stuttering and 21 matched controls. Manual responses involved pressing one of two buttons with the right index finger in response to a left or right pointing arrow and spoken responses involved reading aloud a pseudoword. Participants were instructed to inhibit their responses when an auditory "stop signal" was presented. The timing of the stop signal was determined as the delay at which a participant successfully stopped on 50% of the stop trials. FMRI data obtained in 30 of the participants who stutter and 17 controls were analysed. Group comparisons were made using mixed effects (cluster threshold $Z > 2.3$, $p < .05$ corrected).

Results: We found that PWS were slower to respond to simple 'go' stimuli than PWTF, but there was no difference in stopping behaviour. Our fMRI results were consistent with these behavioural results. The fMRI analysis revealed the expected networks associated with manual response initiation and inhibition previously described. However, all contrasts between the two groups were characterised by overactivity in PWS relative to controls. This overactivity was significantly different for the initiation of responses but not for response inhibition.

Conclusions: One explanation for these results is that PWS are consistently in a heightened inhibition state, i.e. areas of the inhibition network are more active, generally. This interpretation is consistent with predictions from the global response suppression hypothesis (Neef et al., 2015).

5.2 Introduction

Contemporary evidence suggests developmental stuttering is a speech motor disorder with a distinct neural profile (Belyk et al., 2015; Brown et al., 2005; Neef et al., 2015; Watkins et al., 2008). Many brain areas that control speech production show differences, both functionally and structurally, in people who stutter (PWS). Many of these areas are part of cortico-basal ganglia-thalamocortical motor loops involved in movement control (Alm, 2004; Bohland et al., 2010; Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011). One area described as a 'neural signature' of developmental stuttering is the right inferior frontal cortex an area that contributes to the network involved in response inhibition (Aron et al., 2004; Chambers et al., 2007; Xue et al., 2008). It is hypothesized that abnormal inhibitory control may account, in part, for brain differences described in developmental stuttering (Alm, 2004; Hartwigsen et al., 2019; Metzger et al., 2018; Neef, Anwander, et al., 2018; Neef et al., 2015; Xue et al., 2008). Here, a classic inhibition task was used with people who stutter whilst recording functional MRI images to specifically test whether there are differences in the neural control of inhibition.

5.2.1 Right hemisphere over activity in PWS

Hyperactivation in the frontal regions of the right hemisphere is robustly found in imaging work with PWS (Brown et al., 2005; Neef et al., 2015). However, the mechanisms underlying this activity remain unclear. For example, it is unclear whether functional differences reflect general *traits* of developmental stuttering or specifically relate to moments of stuttering (*state* level). Recent evidence suggests that hyperactivation is more associated with state level stuttering: during

dysfluent states relative to fluent ones, there was greater activation of inferior frontal and premotor cortex extending into the frontal operculum, bilaterally (Connally et al., 2018). The right hyperactivation evoked during stuttered moments could reflect an overactive inhibition signal in PWS compared with people who are typically fluent (PWTF). For example, one study attempted to isolate the time course of right inferior frontal gyrus (IFG) activity during speech, from initiation to inhibition of the utterance (Neef et al., 2016). Compared with other regions activated by speaking, including the left IFG and temporal areas, the right IFG showed delayed peak activations, corresponding to the end of utterances. This temporal delay was observed in both PWS and PWTF, but consistent with previous comparisons between groups, the peaks were stronger in PWS. In addition, hyperactivity of rIFG correlated positively with stuttering severity, suggesting that hyperactivation contributes to stuttering (Neef, Anwander, et al., 2018). Combined, imaging evidence suggests a strong link between rIFG activation and stuttering, that is hypothesised to relate to differences in inhibitory control.

5.2.2 Inhibitory control of movement

The right IFG is part of a cortico-subcortical network of areas that controls movement initiation and inhibition in people who are typically fluent (Aron & Poldrack, 2006; Aron et al., 2004). The function and structure of this network can be described in great detail due to recent advances in invasive investigation of key subcortical structures via animal studies and surgery for deep brain stimulation as a treatment for Parkinson's disease. The basal ganglia are a set of highly interconnected nuclei that act via cortico-striatal-thalamo-cortical loops to balance the initiation of desired behaviours and inhibit interfering actions. The communication within these circuits is modulated via dopaminergic neurons. Two pathways are responsible for maintaining the balance between initiation and inhibition of movement. The direct pathway is responsible for initiating

action via disinhibition of the thalamic projections to the motor cortex. Dopamine produced by the substantia niagra binds to D1 receptors on inhibitory neurons that project from the striatum to the globus pallidus. Projections from the globus pallidus internal segment (GPi) subsequently decrease the tonic inhibition of the thalamus, thus increasing signalling to the motor cortex. The indirect pathway is responsible for inhibition of movement. Dopamine, produced in the subthalamic nucleus (STN), binds to D2 receptors on excitatory neurons which increase the tonic inhibition of the thalamus, decreasing signalling to the motor cortex. A third hyperdirect pathway through the basal ganglia involves direct input from the cortex to the STN bypassing the striatum. As the excitatory input from the cortex increases STN firing, which in turn excites the inhibitory output of the GPi, the hyperdirect pathway is thought to provide rapid inhibition of basal ganglia output to the cortex (Nambu, Tokuno, & Takada, 2002). The STN is linked via white matter tracts to the supplementary motor complex (pre-SMA/SMA) and ipsilateral right IFG (Aron et al., 2007), which are also connected via the frontal aslant tract. This circuit may act to provide cortical control over this inhibitory pathway (Aron et al., 2003; Chambers et al., 2007). The involvement of the right IFG in stopping movement is supported by functional imaging results indicating that subjects who inhibit more quickly activate the right IFG and the STN region more (Aron & Poldrack, 2006).

5.2.3 Commonalities between inhibition responses and stuttering

The commonalities between atypical networks in PWS and the inhibitory control network as studied in typical populations support the idea that speech dysfluencies are caused by a global response suppression mechanism which inhibits selection of upcoming speech motor movements (Neef et al., 2015; Neef et al., 2018; Alm, 2004). This could account for characteristic dysfluencies seen in developmental stuttering: prolongations, failure to initiate a motor plan and

repetitions of a sound. However, understanding whether the similar activation profiles share an inhibition mechanism remains to be tested. Recording and imaging subcortical structures to the level of detail described above is not feasible in people who stutter. Based on what is known from invasive methodologies in other populations, it is theorised that the output from the thalamus fails to project appropriate timing cues for the initiation of speech movements to the motor networks, including SMA, premotor/motor cortex and cerebellum (Alm, 2004; Aron et al., 2004; Mink, 1996). Further evidence in support of a role for the basal ganglia or dopamine (or both) in developmental stuttering comes from pharmaceutical and lesion studies. Dopamine antagonists appear to improve fluency (Lavid et al., 1999; Maguire et al., 2000), whereas agonists worsen fluency (Anderson et al., 1999). In addition, increased levels of FDOPA uptake were described in the network of areas implicated in stuttering, including the medial prefrontal cortex, orbitofrontal cortex, insular cortex, auditory cortex as well as the ventral limbic cortical regions (Wu et al., 1997). Patients with neurogenic (acquired) stuttering have lesions encompassing the putamen (striatum), pallidum, cortical motor areas (Heuer et al., 1996), and the thalamus (Van Borsel et al., 2003). Whilst such lesion studies suggest a link between the basal ganglia-cortical circuits and stuttering, the size of the lesions makes it difficult to establish a causal relationship between damage to a specific region and behaviour (Alm, 2004). A key piece of evidence that is missing, is whether PWS have hyperactivity in this network during an inhibition task, independent of speech and stuttering.

5.2.4 The Stop Signal Paradigm

The stop signal task paradigm has been used in conjunction with fMRI to robustly isolate inhibition responses (Aron & Poldrack, 2006; Chevrier, Noseworthy, & Schachar, 2007; Ray Li, Yan, Sinha, & Lee, 2008; Xue et al., 2008). During this task, participants produce a button-press

response to a visual stimulus as quickly as possible. On a small percentage of randomly inserted trials, participants are cued to inhibit their response by an auditory tone (the "stop signal"). The timing of the stop signal is adjusted to determine the interval needed such that participants fail to inhibit their action 50% of the time. This paradigm was adapted to measure inhibition of speech responses. Xue et al., (2008) demonstrated that both motor and spoken response inhibition evokes common neural activity in the right IFG. This suggests that inhibitory control is a domain general process. Using this paradigm, initiation of movements in response to a cue, as well as successful and unsuccessful inhibition of movement responses can be recorded behaviourally and imaged using MRI.

Previous studies used this task behaviourally to test manual response inhibition in adults who stutter and showed that PWS have a longer stop signal reaction time (SSRT) compared with PWTF (Markett et al., 2016). Work using a similar inhibition task, the GO/NO GO task, also showed that children who stutter had a decreased ability to inhibit responses compared with matched controls (Eggers, De Nil, & Van Den Bergh, 2013). This would suggest that PWS have problems enacting an inhibitory response. This is in contrast to the global suppression hypothesis which suggests that PWS overactivate inhibitory responses within the basal ganglia-thalamo-cortical circuits (Neef, Anwander, et al., 2018). Instead, over activity in the basal ganglia–thalamo-cortical network described during speech in PWS could be unrelated to inhibition specifically. Therefore, it is clear that replication of the behavioural studies, alongside fMRI recording during the SSRT task should help to reconcile these two alternative hypotheses.

5.2.5 Neural inhibition response and stuttering

Limited evidence exists directly linking stuttering with neural inhibition. One study recorded function MRI whilst PWS performed a manual GO/NOGO task (Metzger et al., 2018). This study found increased activity in the basal ganglia and thalamus and particularly in the substantia nigra during response preparation. Importantly, task-related activity in the substantia nigra correlated positively with the trait of stuttering severity. In addition, the globus pallidus and the thalamus showed increased network synchronization with the IFG in PWS compared with PWTF (Metzger et al., 2018). Similarly, other work shows a positive correlation between white matter connectivity of the thalamus with right IFG and stuttering severity (Neef, Anwander, et al., 2018). Together, these findings provide evidence for abnormal function of the basal-ganglia-thalamo-cortical network involved in inhibition of manual responses in PWS. Differences in the manual domain suggest differences in inhibitory control beyond speech motor control, which would be consistent with the idea that speech and non-speech movements share an inhibitory control network (Xue et al., 2008). Here, we used fMRI during a stop-signal task to capture manual initiation and inhibition responses of PWS and PWTF.

5.2.6 Aims and hypotheses

The aim of this study was to investigate neural differences related to response initiation and inhibition in PWS using the stop signal paradigm. According to the overactive inhibition hypothesis, shorter SSRT behaviourally and hyperactivation of the right hemisphere inhibition network were expected. Using the manual version of the stop signal task allowed us to address whether differences in inhibitory control are domain general.

5.3 Experiment 1: Pre-scan behavioural task

5.3.1 Subjects

38 adult people who stutter and 21 matched controls participated in the study. Groups were matched for gender, age, years of education and ethnicity (See Table 5.1, below). In the stuttering group, stuttering severity ranged from moderate to very severe as measured by the SSI (Stuttering Severity Instrument-4; Riley 2009) and participants had no diagnosis of other speech or language disorders. Participants had not undergone speech therapy for at least 6 months prior to testing. They had corrected or corrected-to-normal vision and hearing.

Table 5.1 Demographics of participants.

Group means and proportions (%) of group are shown for Gender and Ethnicity. The means and SD are provided for age and years of education.

Variable	PWS	CON
Gender		
Male	32 (84%)	16 (76%)
Female	6 (16%)	5 (23%)
Age	31.5(7.2)	28.6(6.4)
Years of education	16.7(4.2)	18.2(2.6)
Ethnicity		
Arab	1(2.6%)	0
Asian	5(13.%)	5(23.5%)
Black	1(2.6%)	0
White	29(75.4%)	15(71.4%)
Mixed	2(5.2%)	1(4.8%)

5.3.2 Pre-scan task

The stop signal task was run before the scan session in order to determine the stop-signal delay (SSD) to be used during scanning for each participant. The task was identical to the prescan task described in Xue et al., (2008). 240 Go trials and 80 Stop trials were used to estimate the SSD for manual responses. On Go trials, each trial started with a white fixation cross, presented on a grey background for 500 ms. After which, a visual stimulus appeared on the screen for one second. Participants were presented with a left or right facing arrow (< or >). Participants responded by pressing one of two buttons with the right index finger corresponding to the left/right direction of the arrow. The inter-trial delay was two seconds. Stop trials were visually identical to go trials except that an auditory cue (500ms) was played at an interval after presentation of the visual stimulus (arrow). Participants were instructed to respond as fast as possible to the visual stimulus and were told that it would not always be possible to stop in response to the auditory cue. The delay was changed adaptively according to the subject's behaviour. If the participant inhibited successfully on a stop trial, then inhibition was made less likely on the next stop trial by increasing the SSD by 50ms, thus increasing the time that the visual stimulus was on the screen before the stop signal and the likelihood that the participant would begin to respond before the auditory stop signal was presented (i.e. making the stopping more difficult). If the participant failed to inhibit, the SSD was decreased by 50ms, thus giving participants less time to initiate a Go response before the cue was played and the response was more easily stopped or inhibited. The SSD was varied in this way using a staircase algorithm. An individual participant's SSD was computed as the SSD at which the probability of a participant successfully inhibiting on a Stop trial was 50%. This SSD was used during scanning, thereby ensuring that the task was equally difficult for each participant. As SSD was varied to yield a 50% chance of stopping, the stop-signal reaction time (SSRT) was estimable by subtracting average

SSD from the median reaction time (RT) of correct Go responses. The SSRT provides a measure of the speed of the stopping process: a short SSRT indicates a quick stopping process and a long SSRT indicates a slow stopping process (See Figure 5.1, below).

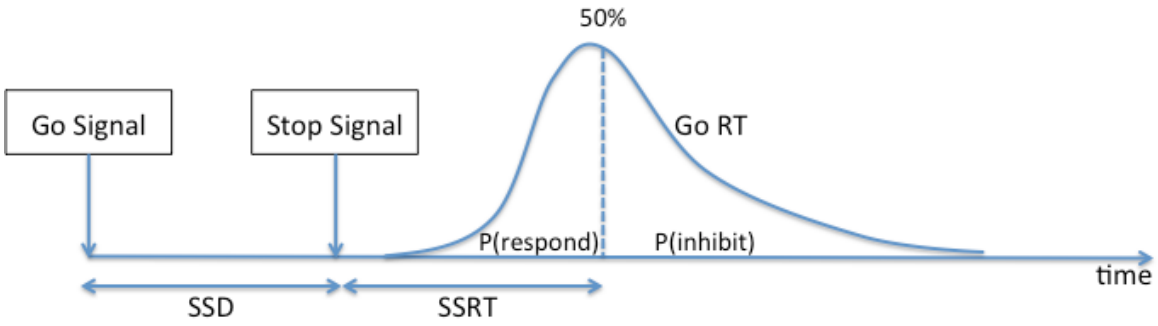


Figure 5.1 Schematic of the Stop Signal Paradigm.

SSD = the time between the go onset and they stop signal. SSRT = the time between the stop signal and the 50% probability of inhibition. Go RT = The distribution of reaction time for go trials.

5.3.3 Behavioural results

The results of the behavioural study are summarised in table 5.2.

Table 5.2 Summary Statistics for pre-scan behavioural task.

Variable	PWS	CON
Go reaction Time	542.41(92.18)	488.61(76.06)
SSD	325.23(122.91)	277.56(98.97)
SSRT	217.18(64.92)	211.05(67.22)
Percent responding on go trials	96.24(5.02)	98.91(0.96)

Group means (standard deviation) are shown. See Figure 5.1 for details of each variable.

Independent t-tests were used to assess the difference between PWS and PWTF for each of the measured variables. All statistical analyses were completed in R using the 'stats' package (R Core Team, 2019).

For the Go trials reaction time, PWS responded significantly more slowly than PWTF ((t(57) = 2.28, $p = 0.027$, d = 0.64). PWS and PWTF showed no difference in SSD (t(57) = 1.53, $p = 0.13$) nor SSRT (t(57)=0.34, $p = 0.73$).

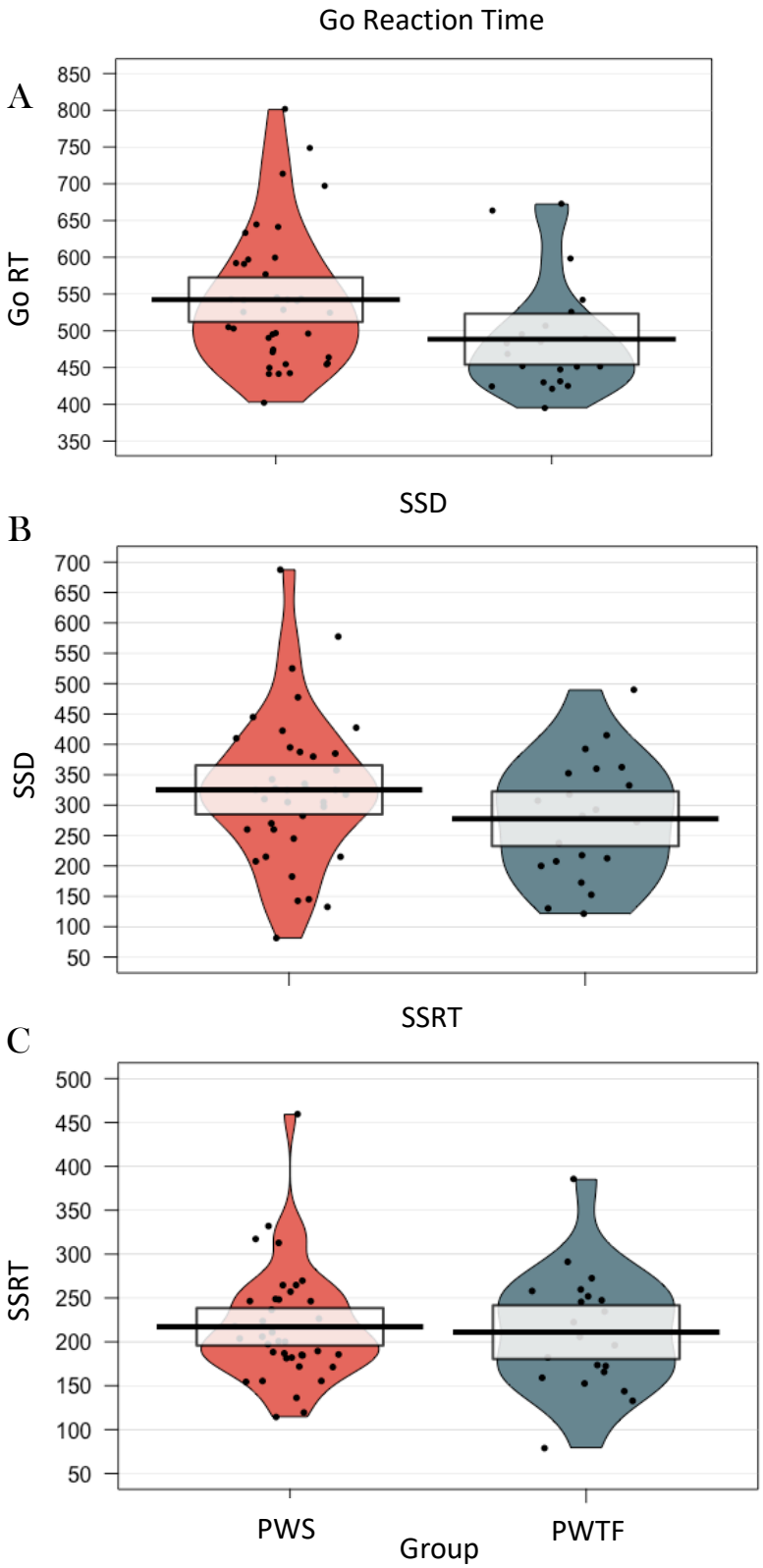


Figure 5.2 Results from the behavioural SSRT task.
Violin plots are shown for the PWS (orange) and PWTF (blue) groups for A) Go Reaction Time; B) Stop Signal Delay; C) Stop Signal Reaction Time. Data points for individual subjects are shown by the small black dots. The group mean is indicated by the solid black line and the 95% confidence interval by the white shaded box. The colour shading indicates the distribution of data for each group.

5.4 Experiment 2: Task fMRI

5.4.1 Subjects

The SSD from the behavioural task was used during scanning to approximate the delay at which participants would successfully stop 50% of the time and fail to stop 50% during stop trials. This approximation did not always result in a near-equal distribution of stopping responses during scanning. Therefore, criteria were set to ensure enough of each trial type was recorded from the participant for analysis: participants needed to produce more than 10/24 successful or unsuccessful stops during the fMRI for the data to be used in the following analyses. Data from two participants (both PWS) failed to meet these criteria. In addition, data from seven participants (five PWS and two CON) were excluded for technical reasons (e.g. button box failure, scanner issues) and two participants (one PWS one CON) were excluded for excessive movement (>2mm average absolute movement).

After these exclusions, data from 30 PWS and 17 CON were analysed.

5.4.2 fMRI SSRT task

The stop signal paradigm was used to assess manual responses as described in Xue et al., (2008). The task consisted of 144 Go and 48 Stop trials. The paradigm in the scanner was the same as described above, except that the staircasing algorithm was replaced with a fixed, individualised, SSD.

5.4.3 MRI data acquisition

Image data were acquired using a 3T Siemens magnetom Prisma scanner using a 64-channel head and neck coil. Echo planar images were acquired with 72, 2-mm isometric slices with multiband acceleration factor of 8 (TR/TE = 720/33, Flip Angle = 53 deg, FOV = 208, in-plane resolution of 2 x 2 mm). High-resolution T1-weighted structural images of the whole brain were also acquired with an MPRAGE protocol (PAT2, 1mm isotropic, TR/TE = 2400/3.98).

5.4.4 Imaging preprocessing and statistics

Data for each participant were preprocessed using standard parameters in FMRIB Software Library (FSL version 6.0.1 http://www.fmrib.ox.ac.uk/fsl, [Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012]). For each subject, the whole-brain T1-weighted image was skull stripped using the Brain Extraction Tool (BET; part of FSL). Functional data were processed at the subject-level using FMRI expert analyses tool (FEAT, v 6.0). A temporal high-pass filter with a cut-off of 90s was used to remove low-frequency fluctuations in the signal. Standard motion correction was applied (MCFLIRT). Data for one PWS and two CON were removed because their average absolute motion (relative to the reference image) exceeded a single voxel width (2mm). The fMRI model at the single subject level consisted of 4 explanatory variables related to the task performance of that individual: 'Go', 'Successful Stop', 'Unsuccessful Stop' and 'Error' (where the subject did not respond on a 'Go' trial) trials. The model was convolved with the double-gamma haemodynamic response function was used and an additional temporal derivative for each of the four explanatory variables was created to account for small variations

in the exact timing of the haemodynamic response across brain areas and among individuals. We also included 6 additional regressors (covariates of no interest) relating to the motion correction: translations and rotations in each of x, y, and z. Data were smoothed with a 5-mm full-width-at-half-maximum Gaussian smoothing kernel. *B*0 unwarping was conducted using the fieldmap images and PRELUDE and FUGUE software running in FSL (Jenkinson et al., 2012). All fMRI volumes were first registered to a reference image (increased SNR and contrast but with same distortions) and then aligned to the individual's structural scan using brain boundary registration (BBR), implemented using FMRIB's Linear Image Registration Tool (FLIRT). They were then registered to 2-mm MNI standard space using FMRIB's Nonlinear Image Registration Tool (FNIRT) for group analyses.

Group comparisons were implemented using FMRIB's Local Analysis of Mixed Effects stage 1 (Woolrich et al., 2004). For group averages, results are reported using a cluster-forming threshold $Z > 3.1$, and extent-threshold of $p < .05$ corrected. To protect against possible false negative errors in the between-group contrasts, we used a reduced cluster-forming threshold of $Z > 2.3$ and extent threshold of $p < .05$ (corrected).

5.4.5 fMRI results

5.4.5.1 Go trials

The controls showed focal activation of the left precentral gyrus at the level of the hand representation, the left putamen extending to the opercular cortex, the SMA and extensively in

the cerebellum bilaterally. This pattern of activation was consistent with the task which involved a simple button press with the right index finger in response to the visually presented arrow. There was also activity bilaterally in the occipital cortex evoked by the visual stimulus.

In contrast to the rather focal pattern of activity in the controls, PWS had extensive and widespread activation of precentral gyrus, the SMA, the putamen and frontal operculum, the cerebellum, all bilaterally. The left postcentral gyrus and supramarginal gyrus bilaterally were also robustly activated. There was also activity in the anterior portion of the middle frontal gyrus bilaterally. Visual cortex activity extended from the pole to include the lateral occipital cortex bilaterally.

The contrast between groups confirmed that this pattern of widespread overactivity in PWS was statistically significant. PWS had significantly greater activity relative to controls in the inferior frontal gyrus, caudate nucleus and putamen bilaterally, and in the left precentral cortex and parietal operculum (see Figure 5.4).

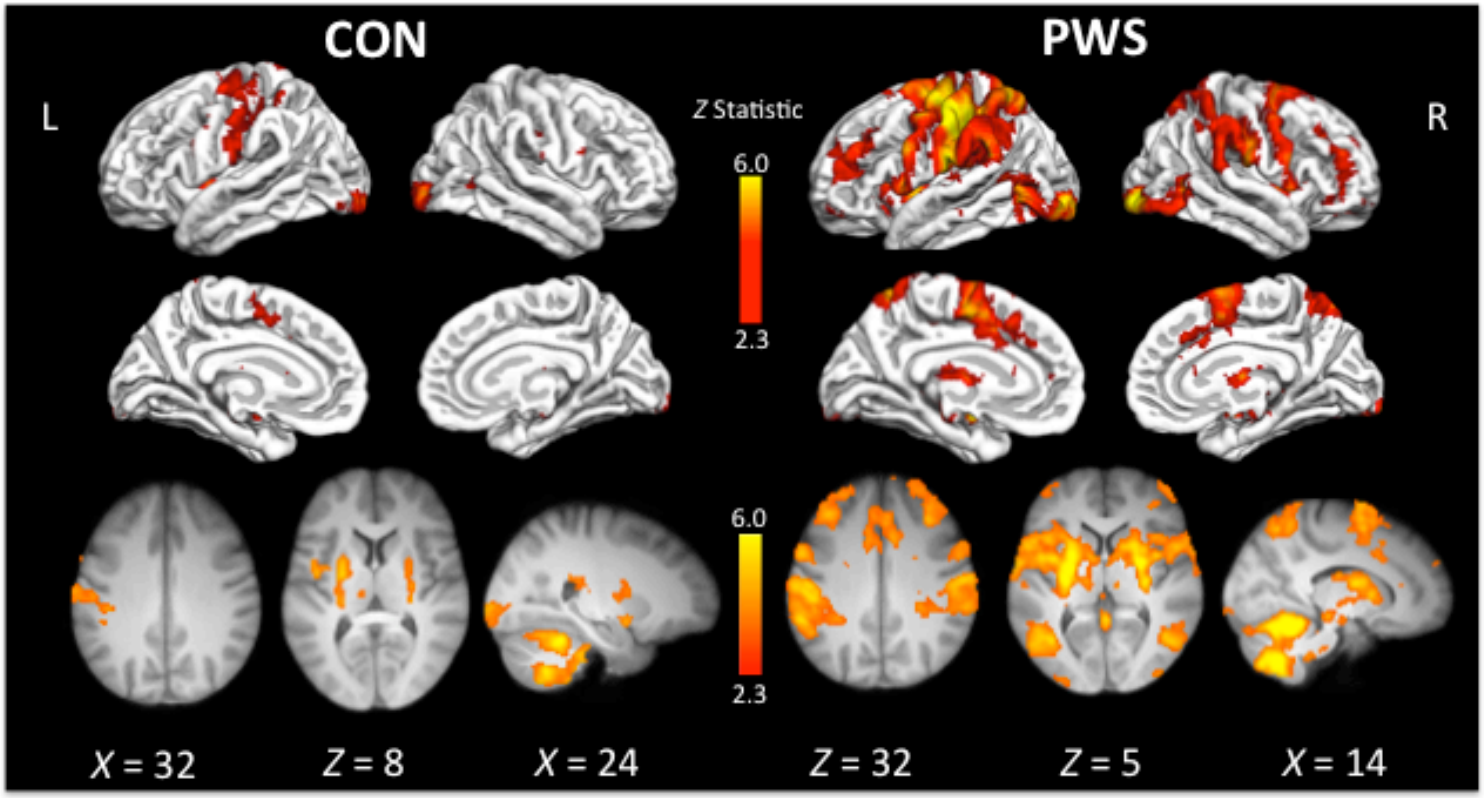


Figure 5.3 Activity during 'go' trials for PWTF and PWS.

Coloured areas indicate statistical maps (thresholded at Z>2.3 for visualisation purposes) overlaid on the cortical surface using FreeSurfer or on slices through the brain volume at the coordinate indicated below each image. CON = people who are typically fluent. PWS = people who stutter. L – left; R – right. See Tables 5.3 and 5.4 for a list of areas significantly activated for each group.

Table 5.3 Activation peaks and coordinates for peaks in clusters significantly activated in PWTF during 'go' trials.

The cluster size, peak Z statistic, and MNI coordinates of selected peaks are provided.

Cluster location	Number of voxels	z	X	Y	Z
Supplementary motor area	133	4.49	0	-2	72
Left precentral gyrus	1177	4.44	-30	-6	70
Left postcentral gyrus		4.42	-54	-28	52
Superior parietal lobe		4.35	-26	-48	72
Left putamen	417	4.81	-24	-6	8
Insula		4.4	-38	0	4
Left operculum		3.99	-44	-2	18
Left globus pallidus	159	4.61	-26	-18	0
Right cerebellum	3212	5.66	24	-48	-26
Left cerebellum		4.29	-30	-58	-55
Right occipital pole	262	5.31	30	-92	-4
Left occipital pole	1254	4.89	-28	-96	-8

Table 5.4 Activation peaks and coordinates for peaks in clusters significantly activated in PWS during 'go' trials.

See Table 5.3 for details.

Cluster location	Number of voxels	z	X	Y	Z
Right middle frontal gyrus	636	4.63	44	44	24
Left middle frontal gyrus	691	4.46	-38	34	32
Cortical and subcortical motor areas	22195				
Right putamen		6.89	26	-2	4
Supplementary motor area		6.09	0	-4	46
Left putamen		7.57	-26	-6	6
Left precentral gyrus		7.09	-50	-18	56
Left postcentral gyrus		6.86	-42	-26	48
Right postcentral gyrus	3143	5.2	34	-40	36
Cerebellum and occipital lobe	13938	7.91	14	-52	-20
Left cerebellum		6.32	-31	-49	-28
Right cerebellum		7.34	18	-62	-48
Right occipital pole		7.41	32	-92	-4

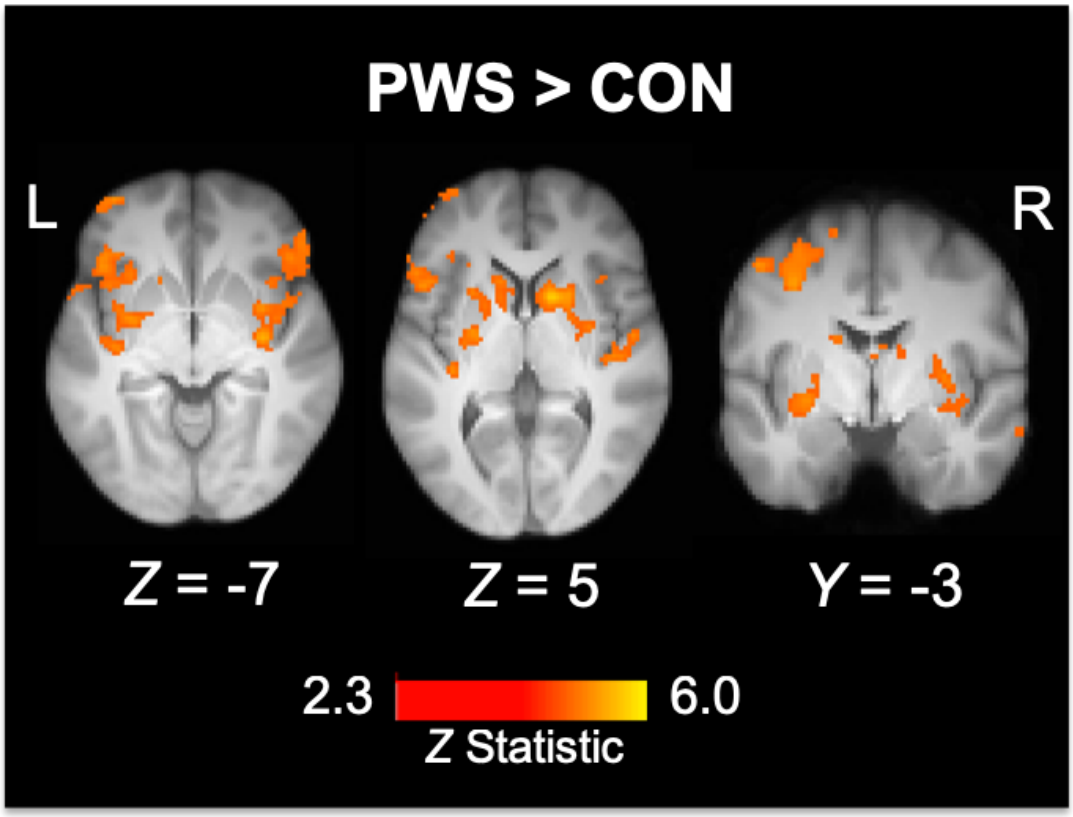


Figure 5.4 Areas with significantly greater activity in PWS than PWTF during 'go' trials.

See legend to Figure 5.3 for details. See Table 5.5 for a list of areas significantly activated for this contrast.

Table 5.5 Activation peaks and coordinates for peaks in clusters significantly activated in PWS more than PWTF during 'go' trials.

See Table 5.3 for details.

Cluster Location	Number of voxels	z	X	Y	Z
Left inferior frontal gyrus (orbitalis)	1483	3.96	-44	26	-10
Left inferior frontal gyrus (opercularis)		3.53	-50	16	2
Right striatum and operculum	1678	4.78	14	10	4
Right inferior frontal gyrus (triangularis)		3.47	52	24	-2
Right insula		3.69	34	6	-14
Right caudate nucleus*		3.5	14	4	16
Right putamen		4.2	34	-12	-4
Left striatum	698				
Left putamen		3.77	-22	0	-4
Left caudate nucleus		3.34	-14	6	14
Left precentral gyrus*	831	4	-36	-2	44
Left parietal operculum	484	3.64	-60	-24	24
Right medial parietal cortex	397	4.18	12	-66	56

*survived cluster thresholding at z>3.1 for the group contrast

5.4.5.2 Successful stop trials

On the 'successful stop' trials, PWTF activated the middle frontal gyrus, frontal operculum extending to putamen, postcentral gyrus, supramarginal gyrus, and cerebellum bilaterally, and the SMA extending to the cingulate motor area. As for the 'go' trials, the pattern of activation in PWS for the successful stop trials was extensive and looked like an amplified version of the

network seen in controls. When the two groups were contrasted, this pattern of overactivity in PWS was not significantly different to that in controls.

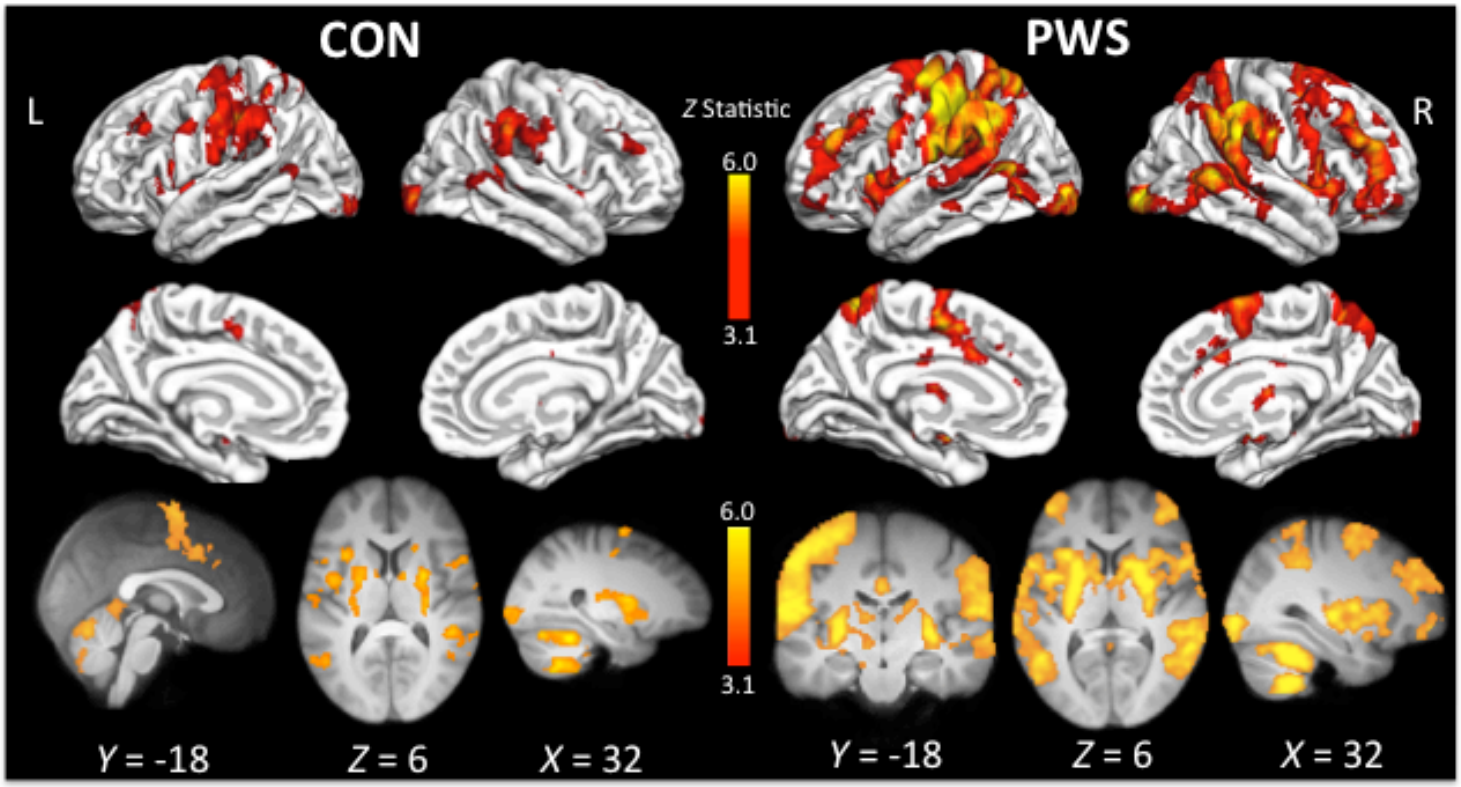


Figure 5.5 Activity during 'successful stop' trials.

Coloured areas indicate statistical maps (thresholded at Z>3.1) overlaid on the cortical surface using FreeSurfer or on slices through the brain volume at the coordinate indicated below each image. L – left; R – right. See Tables 5.6 and 5.7 for a list of areas significantly activated for each group.

Table 5.6 Activation peaks and coordinates for peaks in clusters significantly activated in PWTF during 'successful stop' trials.

See Table 5.3 for details.

Cluster Location	Number	z	X	Y	Z
Right middle frontal gyrus	429	4.51	40	40	30
Left middle frontal gyrus	305	4.68	-38	30	38
Right striatum and operculum	1603				
Right frontal operculum		5.05	42	14	-2
R inferior frontal gyrus (opercularis)		4.93	56	12	0
Right insula		5.63	42	8	-2
Right putamen		5.25	26	0	10
Left striatum and operculum	2444				
L frontal operculum		5.19	-32	16	14
L inferior frontal gyrus (opercularis)		4.41	-48	12	11
L insula		5.34	-40	2	4
L putamen		4.95	-28	-16	5
Right dorsal motor cortex	1283				
R cingulate motor area		3.92	2	13	41
R precentral gyrus		5.09	36	-4	64
R SMA		4.88	2	-6	74
Left sensorimotor cortex	5545				
L precentral gyrus		5.58	-30	-6	70
Left Postcentral Gyrus		5.17	-42	-28	42
Left supramarginal gyrus		5.4	-60	-36	22
Right inferior parietal	3170				
R postcentral gyrus		4.55	62	-14	36
R supramarginal gyrus		5.2	64	-36	36
Cerebellum	7174				
Right cerebellum		6.09	26	-48	-26
Left cerebellum		5.66	-46	-61	-28
Right occipital pole	333	5.5	30	-92	-4

Table 5.7 Activation peaks for PWS during successful stop trials.

Using Z>3.1 resulted in clusters of very large extent spanning multiple anatomical areas. We report locations for these clusters using Z>4.3 cluster forming threshold for clarity (Labelling truncated for clusters with < 50 voxels in extent). The cluster size, peak Z statistic, and MNI coordinates of selected peaks are provided.

Cluster Location	Number	z	X	Y	Z
R middle frontal gyrus	1045	6.01	42	48	24
R frontal pole	118	5.78	22	44	-12
L middle frontal gyrus	435	6.28	-40	36	34
R striatum and operculum	2461				
R inferior frontal gyrus		5.84	57	15	-2
R insula		7.15	46	14	-6
R putamen		7.12	28	-2	8
L striatum and operculum	2518				
L operculum/insula		6.61	-46	14	-6
L inferior frontal gyrus		6.47	-52	12	2
L putamen		7.35	-24	2	6
L medial and lateral cortex	8958				
L cingulate gyrus		5.2	-5	5	42
L SMA		6.1	-2	-4	55
L operculum		7.3	-64	-22	16
L postcentral gyrus		7.39	-42	-28	48
L supramarginal gyrus		6.7	-61	-47	36
R precentral gyrus	108	4.96	62	8	26
L precentral gyrus	93	5.41	-58	6	30
Cerebellum	6342				
R cerebellum		7.9	32	-48	-48
L cerebellum		7.19	-32	-58	-12
R supramarginal gyrus	4371	6.62	64	-36	30
R postcentral gyrus		5.99	59	-16	30
R superior parietal lobe	63	5.35	12	-54	56
L lateral occipital cortex	431	6.04	-52	-68	2
R occipital pole	369	7.12	32	-92	-4
L occipital pole	474	6.39	-26	-100	-6

5.4.5.3 Unsuccessful stop trials

For the 'unsuccessful stop' trials, controls showed activity in the left postcentral gyrus, putamen and thalamus, and bilaterally in the supramarginal gyrus, SMA extending to cingulate motor cortex, frontal opercular cortex, and cerebellum. In PWS, a similar but more robust pattern of activation was seen. These two patterns of activation were not significantly different, however.

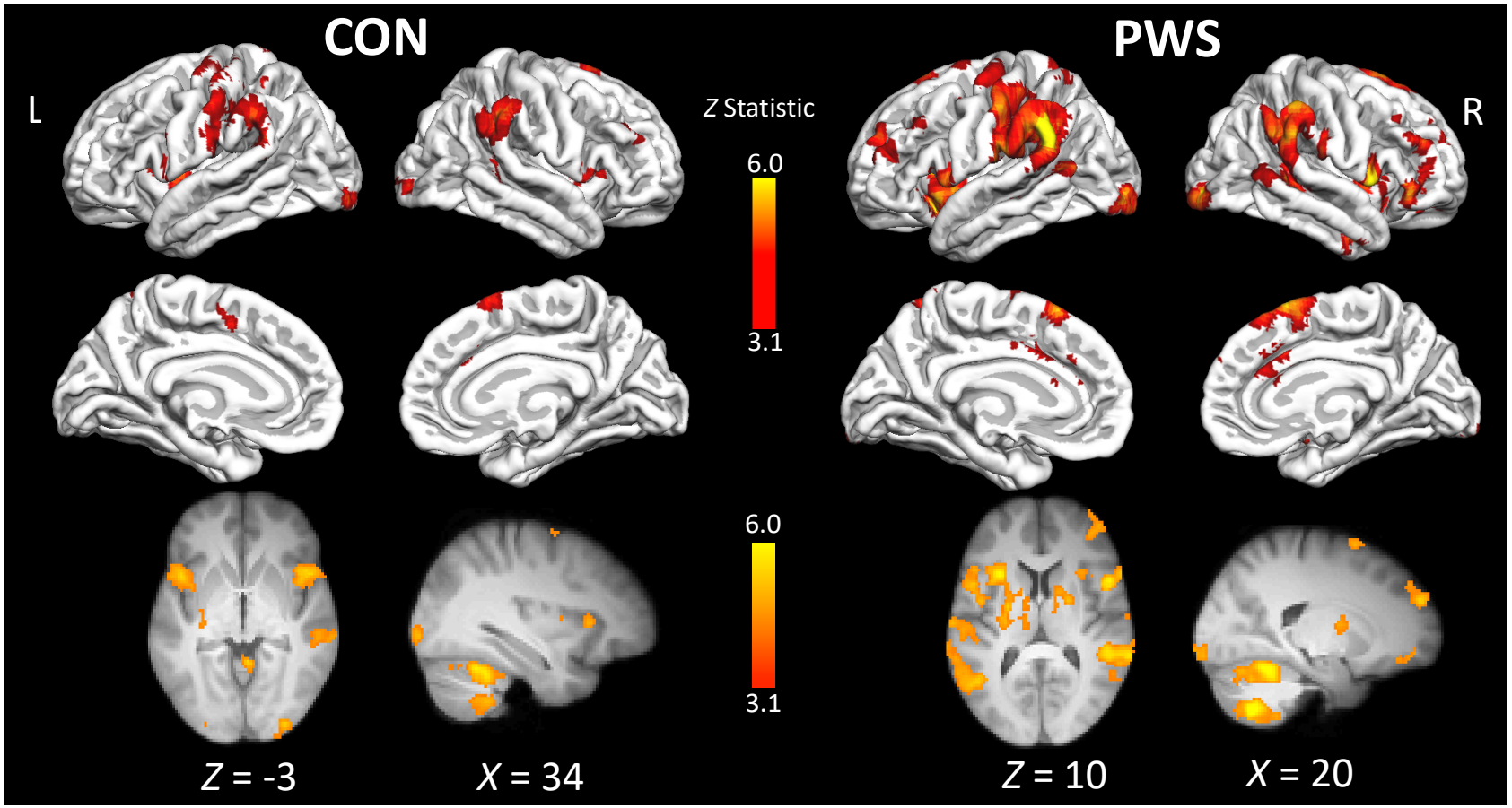


Figure 5.6 Activity during 'unsuccessful stop' trials.

See legend to Figure 5.5 for details. See Tables 5.8 and 5.9 for a list of areas significantly activated for each group.

Table 5.8 Activation peaks and coordinates for peaks in clusters significantly activated in PWTF during 'unsuccessful stop' trials.

See Table 5.3 for details.

Cluster Index	Number of	z	X	Y	Z
R middle frontal gyrus	220	4.54	42	42	30
R frontal operculum	741	5.15	50	14	-4
L frontal operculum	1253	5.34	-46	12	-6
Medial frontal cortex	1616				
L SMA		5.38	2	-6	74
L Cingulate cortex		4.18	2	17	40
L putamen	182	4.45	-28	-22	2
L sensorimotor cortex	3484				
L postcentral gyrus		5.16	-56	-28	48
L supramarginal gyrus		5.13	-57	-45	26
R supramarginal gyrus	1532	5.41	56	-40	36
L cerebellum	1776	4.95	-38	-50	-32
R cerebellum	3230	5.69	34	-54	-26

Table 5.9 Activation peaks and coordinates for peaks in clusters significantly activated in PWS during 'unsuccessful stop' trials.

See Table 5.3 for details.

Cluster Index	Number of	z	X	Y	Z
L middle frontal gyrus	510	4.82	-26	54	26
R middle frontal gyrus	121	4.32	26	46	-10
L middle frontal gyrus	115	4.15	-40	34	34
L frontal opercular cortex	3319	7.38	-46	14	-4
L putamen		4.91	-24	-6	10
R frontal opercular cortex	3839	6.71	54	12	8
R putamen	202	4.66	22	-2	10
L sensorimotor extending to	9979	7.52	-60	-46	34
SMA		4.92	0	20	61
Cingulate cortex		5.25	0	20	40
L parietal operculum		5.98	-60	-22	18
L supramarginal gyrus		7.04	-62	-46	30
R supramarginal gyrus	4094	6.21	62	-46	30
L cerebellum	1956	5.71	-34	-58	-56
R cerebellum	4660	6.95	20	-64	-50

5.5 Discussion

We tested wither there were differences in the neural control of the initiation and inhibition of a manual response in people who stutter (PWS) and people who are typically fluent (PWTF). 38 PWS and 21 PWTF completed the behavioural version of the manual stop signal task (Xue et al., 2008). Of these participants, we also compared fMRI task data in 30 PWS and 17 PWTF. During the task, participants responded to a visual stimulus (left or right arrow) with their right index finger. On randomly inserted trials, participants heard an auditory cue, which indicated they should inhibit their response. Previous work suggests that PWS have an overactive response suppression mechanism (Neef et al., 2018). According to the overactive inhibition hypothesis, shorter SSRT and hyperactivation of the right hemisphere inhibition network were expected. For the behavioural task, PWS had longer reaction times on 'go' trials than PWTF. There was no significant difference in the speed of the stopping process (SSRT). The fMRI results help to understand the behaviour. During 'go' trials, both groups activated the expected motor control areas consistent with the task demands (a simple button press in response to a visual stimulus). In contrast to the rather focal pattern of activity in the controls, however, PWS had extensive and widespread activation for performance of this simple task. PWS showed significantly more activation than PWTF in the inferior frontal gyrus, caudate nucleus and putamen bilaterally, and in the left precentral cortex and left parietal operculum. There was a similar pattern of activation during 'successful stop' trials, which also included activation of the supramarginal gyrus and cingulate cortex. As for the 'go' trials, the pattern of activation in PWS in the successful stop trials

looked like an amplified version of that seen in PWTF, but these differences were not statistically significant.

Overall, these results provide evidence for differences between PWS and PWTF even during a simple 'go' trial. PWS show a pattern of overactivation for both 'go' and 'stop' trials that corresponds to the inhibitory control network (Aron et al., 2007, 2004).

5.5.1 Behavioural results

5.5.1.1 Stopping Response

The global suppression hypothesis predicts that PWS should have shorter stopping responses due to a globally heightened inhibition signal (Neef, Anwander, et al., 2018). Our results suggest that whilst PWS are slower to initiate a response (go reaction time), the stopping response (SSRT) was not different to PWTF. This suggests that PWS do not show differences in the time it takes to inhibit a manual response. The behavioural results of our study contrast with those from a previous study that also employed the manual stop signal task with PWS (Markett et al., 2016). The previous study found that PWS had longer stopping responses (SSRTs) than PWTF. It is unclear why our results contrast with this previous study.

5.5.1.2 Go Response

The longer reaction times for 'go' responses in PWS found in the current study could be explained in two ways. One explanation may be that PWS have greater difficulty enacting a response under temporal uncertainty. For example, the previous study (Markett et al., 2016)

used two tasks to estimate 'go' reaction times: one task had 'go' trials only and used fixed inter-trial intervals, providing strong temporal predictability for when a 'go' response was required. The other task involved trials with varied inter-trial-intervals, which provide less temporal predictability. PWS only showed longer reaction times when the timing of the trials was not predictable (Markett et al., 2016). The authors suggest that this difference may be due to problems relying on internally generated timing compared with the externally generated timing provided by the predictability of the fixed inter-trial-intervals (Alm, 2004; Markett et al., 2016). In the current study, a fixed inter-trial-interval was used, however 'go' and 'stop' trials were presented in a random order, which introduced temporal uncertainty. Therefore, this result is in accordance with previous work on temporal uncertainty and may be the result of internal cueing difficulties in PWS.

Alternatively, PWS may show longer reaction times because they were in a state of heightened inhibition as the task demands required enacting a stopping response and might have prevented them from generating a response as quickly as PWTF. This would support the global suppression hypothesis (Neef, Anwander, et al., 2018; Neef et al., 2016). Nevertheless, the thresholding we implemented was adaptive so there was no benefit of being slower to perform the 'go' response to improve the success of stopping responses and participants were encouraged to perform the task as quickly as possible. Furthermore, the lack of difference in both the SSD and the SSRT during the stop trials suggests that inhibition acted to suppress go responses, rather than over-exerting stopping responses. Our behavioural results cannot distinguish between these two hypotheses.

5.5.2 fMRI results

5.5.2.1 'Go' responses

During 'go' responses PWTF showed the expected, focal, activation of the left precentral gyrus (encompassing the hand area), left putamen extending to the opercular cortex, the SMA and the cerebellum bilaterally, which is consistent with performing a button press with the right index finger. Compared with PWTF, PWS showed significant bilateral overactivation of areas comprising the typical movement 'inhibition' network during 'go' trials. These areas include the inferior frontal gyrus, caudate nucleus and putamen bilaterally as well as the left precentral gyrus (encompassing the hand area). One explanation for these results (as for the behavioural data) is that PWS are consistently in a heightened inhibition state, i.e. areas of the inhibition network are more active, generally. This interpretation is consistent with predictions from the global response suppression hypothesis (Neef, Anwander, et al., 2018; Neef et al., 2015) and previous work that showed hyperactivity in PWS in the basal ganglia, thalamus and substantia nigra during response preparation in a Go/NoGo task (Metzger et al., 2018). An alternative explanation is that the stuttering participants were in a higher state of arousal (possibly due to increased desire to perform the task well, or in response to being scanned). This arousal may cause general over activation of the areas involved in the task. However, this latter interpretation is unlikely to explain these results. There was not simply an amplification of all areas seen in PWTF, specifically, the right IFG was not active in PWTF but was active in PWS. The hypothesised importance of the right IFG in inhibition makes the former hypothesis more likely.

5.5.2.2 'Stop' responses

5.5.2.2.1 Right hemisphere activation for stopping

Previous reports emphasize the important role of the right IFG in the control of stopping behaviour (Aron et al., 2007, 2003, 2004; Aron & Poldrack, 2006; Xue et al., 2008). Our results indicate that PWTF activated the right IFG, operculum and insula during stopping responses, but not during 'go' responses, supporting the idea that this area is selective for stopping behaviour in the typical brain. PWS, on the other hand, activated right frontal regions (including IFG extending to the insula) during both 'go' and 'stop' trials. Accordingly, during 'go' trials, PWS activated right IFG significantly more than PWS. This indicates that the right IFG is active more generally in PWS, again in accord with the global suppression hypothesis (Metzger et al., 2018; Neef, Anwander, et al., 2018; Neef et al., 2011). However, it is important to note that although there were qualitative differences in the amount of activation during stopping behaviour between PWS and PWTF (see Figures 5.5 and 5.6), these differences failed to reach statistical significance at conventional thresholds ($Z > 3.1$, and to check for false negatives, we also reduced the threshold to $Z > 2.3$ and found no differences). Taken together, this work supports the idea that PWS activate the right frontal regions irrespective of the type of response, but that the degree of activation during 'stop' trials was not statistically different to controls.

5.5.2.2.2 Other brain areas involved in stopping behaviour

Whilst the right IFG has been a particular focus of the inhibition literature, it sits within a network of cortical-subcortical regions that carefully balance initiation and inhibition behaviour. During successful 'stop' trials, PWTF also activated the putamen, postcentral gyrus, supramarginal gyrus,

and cerebellum bilaterally, and the SMA extending to the cingulate motor area. These areas have been implicated in the inhibition literature. The putamen is part of both the direct and indirect subcortical pathways that interface between the cortex (rIFG, SMA) and the subthalamic nucleus and thalamus to balance excitatory and inhibitory control (Alm, 2004; Burghaus et al., 2006; Giraud et al., 2008). The supramarginal gyrus was also activated in the inhibition of manual and spoken responses (Xue et al., 2008). Finally, the cingulate cortex was implicated in the cognitive control of inhibition. For example, the cingulate motor area was robustly activated in an effector specific way when participants inhibited a congruent response in favour of a incongruent response (Paus, Petrides, Evans, & Meyer, 1993). This implicates the cingulate cortex in the control of the balance between the selection of motor responses and active suppression of others (Paus, 2001; Paus et al., 1993).

5.5.2.2.3 Why were there no significant differences between groups for stopping?

The lack of statistical difference between the groups during 'stop' trials may reflect similar inhibitory control for stop trials in PWS and PWTF. This is against our prediction, based on the global suppression hypothesis, that PWS would show overactivity in key regions of the stopping network. However, visual inspection shows clear qualitative differences between the patterns of neural activation of stopping responses between PWS and PWTF, with PWS showing an amplified version of the controls. Therefore, while there are no differences that survive statistical thresholding, it cannot be ruled out that there are small differences between groups, or that other factors limit our ability to detect a significant difference between groups. One reason may relate to the design of the study. An event-related fMRI design enables us to randomise the presentation of the 'go' and 'stop' trials so that participants do not know which trial to expect. However, a large number of trials are needed compared with classic block designs. There were a large

number of 'go' trials (144) but because the task requires stop trials to be unpredictable and in the minority, there were fewer stop trials (48), which by using the subject-specific stop-signal delay were expected to yield 50% successful stops (~24) and 50% unsuccessful stops (~24). This reduced the power to detect differences between groups and may explain why we had sufficient power to detect group differences on the 'go' trials but not the 'stop' trials.

Another factor is variability within the groups. Stuttering populations are known to show a lot of individual differences in studies (Yairi & Ambrose, 2013). A large sample of PWS (31) should have helped to compensate for variance within the sample.

5.5.3 Conclusions

In summary, we found that PWS were slower to respond to simple 'go' stimuli than PWTF, but there was no difference in stopping behaviour. Our fMRI results were consistent with these behavioural results. PWS showed significant overactivity of the inhibition network even during 'go' trials, which supports the idea of a global suppression mechanism in PWS. In addition, there were qualitative differences in the neural stopping response between groups, with PWS appearing to overactivate compared to PWTF. However, it must be stressed that these differences did not pass statistical significance, and that the study may have been underpowered to detect them. Overall, this study offers tentative support to the global suppression hypothesis of stuttering.

6 Transcranial Direct current stimulation does not modulate performance on a tongue twister task.

6.1 Abstract

Background: TDCS modulates cortical excitability in a polarity-specific way. When used in combination with a behavioural task, it can also alter performance. Previously, tDCS modulated the performance of older adults on a complex speech motor learning task, which involved repetition of tongue twisters (Fiori et al., 2014).

Objective: We aimed to replicate this finding in healthy young participants and to extend it by measuring tDCS-induced changes in motor excitability using transcranial magnetic stimulation and motor-evoked potentials elicited in the lips.

Method: In a double-blind randomized sham-controlled study, three groups of 20 participants received: 1) anodal tDCS to the left IFG/LipM1 and cathodal tDCS to the right hemisphere homologue; or 2) cathodal tDCS over the left and anodal over the right; or 3) sham stimulation. Participants heard and repeated tongue twisters and matched simple sentences before, during and 10 minutes after the stimulation. Motor excitability was measured before and immediately after the tDCS.

Results: The improvement in performance of tongue twister repetition from baseline to after stimulation was significantly greater than for the simple sentences but did not differ among the three groups. Motor excitability significantly decreased to a small but similar extent across the three groups.

Conclusions: TDCS did not modulate performance on a complex articulation task in healthy young adults. TDCS applied concurrently with task learning also failed to modulate motor excitability in expected ways. TDCS may be most effective in brains where brain function is sub-optimal due to age-related declines or pathology.

6.2 Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate cortical excitability. tDCS exerts its effect by passing a weak electric current between two electrodes placed on the scalp. This current induces polarity-specific modulation such that the anode up-regulates, and the cathode down-regulates local cortical excitability (Bikson & Rahman, 2013; Nitsche & Paulus, 2000). The electrophysiological effects of tDCS can be demonstrated in the motor cortex by measuring changes in excitability via changes in the size of motor evoked potentials (MEPs) recorded from muscles of interest in response to single pulse transcranial magnetic stimulation (TMS) over the cortical representation (Stagg & Nitsche, 2011). Specifically, when targeting the representation of the hand in primary motor cortex (M1), the size of the MEP elicited by TMS in the contralateral hand muscles was increased by anodal tDCS (a-tDCS), and decreased by cathodal tDCS (c-tDCS) relative to sham stimulation (Nitsche et al., 2003; Stagg et al., 2009)

When used in combination with a behavioural task, a single session of tDCS can modulate performance. For speech production specifically, there is some evidence to suggest that tDCS can modulate performance in neurologically intact speakers (Buchwald et al., 2019; Deroche et al., 2017; Lametti et al., 2018). Previously, tDCS modulated performance on a task involving the repetition of tongue twisters (Fiori et al., 2014). Such sentences have complex articulation and their production often results in speech errors that are commonly seen in populations with speech pathologies (Wilshire, 1999). Three groups of healthy older adults received a-tDCS or c-tDCS (both 2mA; 20 mins) or sham stimulation with the active electrode over the left IFG and the inert electrode over the contralateral frontopolar cortex. Participants' response times and

accuracy in repeating tongue twisters were successfully modulated during stimulation: a-tDCS significantly increased accuracy and reduced response times relative to baseline measures, whereas c-tDCS significantly reduced accuracy and increased response times from baseline and sham had no effect. A recent study failed to replicate this behavioural effect (Wong, Chan, Ng, & Zhu, 2019).

Here, we aimed to replicate the previously reported effects of tDCS on tongue twister repetition in healthy young adults and extended the design to include measures of changes in motor excitability before and after tDCS. In the current study, tDCS electrodes were placed over the ventral portion of motor cortex in each hemisphere encompassing the lip representation in M1, premotor and prefrontal cortex. Single pulses of transcranial magnetic stimulation were applied over the representation of the lips in the left M1 to elicit MEPs in the contralateral orbicularis oris muscle. This allowed us to gain more insight into the cortical effects induced by tDCS alongside behavioural outcomes in the same individuals, thus providing more sensitive information about the individual variability of cortical responses to tDCS (Chew, Ho, & Loo, 2015; Guerra, López-Alonso, Cheeran, & Suppa, 2018). The degree to which cortical excitability changes (as indexed by changes in MEP size) could predict changes in behaviour is unknown. Such a relationship could be an important consideration for the use of tDCS as a therapeutic tool. For example, participants could be tested for their suitability for tDCS treatments based on cortical measures of tDCS-induced modulation.

Our study is a conceptual replication in which we aimed to replicate the findings of a previous study (Fiori et al., 2014) in a different population. It is not an exact replication as we made several important changes to the protocol (discussed below).

The study design and analysis plan were pre-registered on the Open Science Framework (https://osf.io/p84ys/).

6.3 Methodology

6.3.1 Sample size

To determine group sample sizes, we estimated an effect size based on graphs presented in (Fiori et al., 2014) for comparing pairs of groups on the change in performance from baseline. We determined that 20 participants per group (n=60) were required based on a moderate effect size of Cohen's d = 0.8 (Fiori et al., 2014) with 80% power at the standard .05 alpha error probability (for a directional t-test). This sample size was double that of the previous study (Fiori et al., 2014); n=10 per group).

6.3.2 Participants

Seventy-one healthy participants were recruited. They were all right-handed, native English speakers with normal or corrected-to-normal vision and normal hearing. We were unable to reliably elicit MEPs at a comfortable stimulation threshold in 11 participants. The remaining 60 participants were aged between 18 and 42 years (mean = 22.3, SD = 4.85); there were 30 men and 30 women.

The University of Oxford Central University Research Ethics Committee approved the study. Participants gave informed written consent to participate in the study, in accordance with the Declaration of Helsinki, and with the procedure approved by the committee.

6.3.3 Design

The study was a double-blind randomized controlled study. Block randomization (block size 6) was used to assign 60 participants to one of four stimulation configurations with an allocation ratio of 2:1 (1mA tDCS with either anode on left or cathode on left, 20 participants each; sham with either anode on left or cathode on left, 10 participants each). Men and women were randomized separately to ensure equal genders in all groups. The researchers were blinded to the allocation of group by using the 'study mode' of the stimulator (NeuroConn GMbH, Ilmenau, Germany). A member of the research group who was not involved in the study assigned a 5-digit code to each participant. The link between the code and the stimulation group was not revealed until all 60 complete data sets were collected.

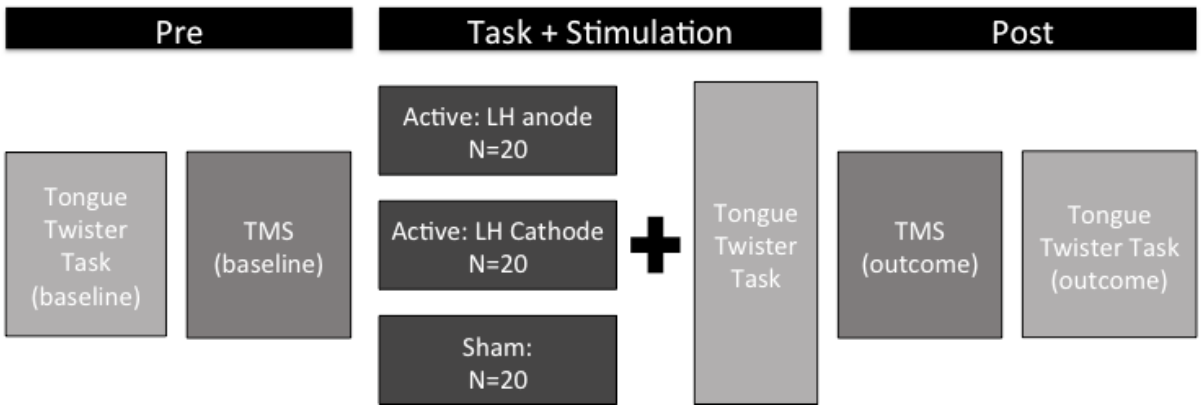


Figure 6.1 Study Design

The stimulation site and motor threshold were determined at baseline and 20 MEPs obtained. The tongue-twister task involved repetition of 36 tongue twisters and 36 simple sentences. The stimulation (anodal, cathodal and sham) was applied concurrently with the task. Twenty MEPs were obtained at the end of the stimulation period and the task was repeated again without stimulation.

6.3.4 Procedure

6.3.4.1 Tongue Twister Task

36 novel tongue twisters (7 or 8 syllables) were taken from a previous published set (Fossett, McNeil, Pratt, Tompkins, & Shuster, 2016). For each tongue twister, a corresponding simple sentence was created that did not contain difficult articulation. To achieve this, one word was retained from the tongue twister and all other words were replaced by a word with the same number of syllables and syntactic class but without difficult articulation. For example, "Chad bravely wore Anne's little shoes" was created to match the tongue twister "Brad bravely broke Brooke's brittle blades". A female, native-English speaker was recorded speaking the tongue twisters and control sentences in a soundproof booth. Recordings were presented via TMS-compatible insert headphones (Etymotic, Elk Grove Village, IL, USA).

For each trial, participants were instructed to repeat the sentence immediately after the cessation of the audio recording within a four and a half second response window. The task comprised three blocks of 24 sentences (12 tongue twisters and 12 simple sentences, presented in a randomised order). After each block, participants took a 30-s break. The duration of the task was 13 minutes. Participants practised the task on three simple sentences prior to the first run.

6.3.4.2 Behavioural Pilot Results

A pilot experiment was conducted to measure behavioural responses to the stimuli. Ten participants completed the sentence repetition task, only. Two outcome variables were assessed: response time (from the offset of the auditory stimulus until the end of the participant's response) and accuracy (percentage of syllables produced correctly). Pilot data are shown in Figure 6.2.

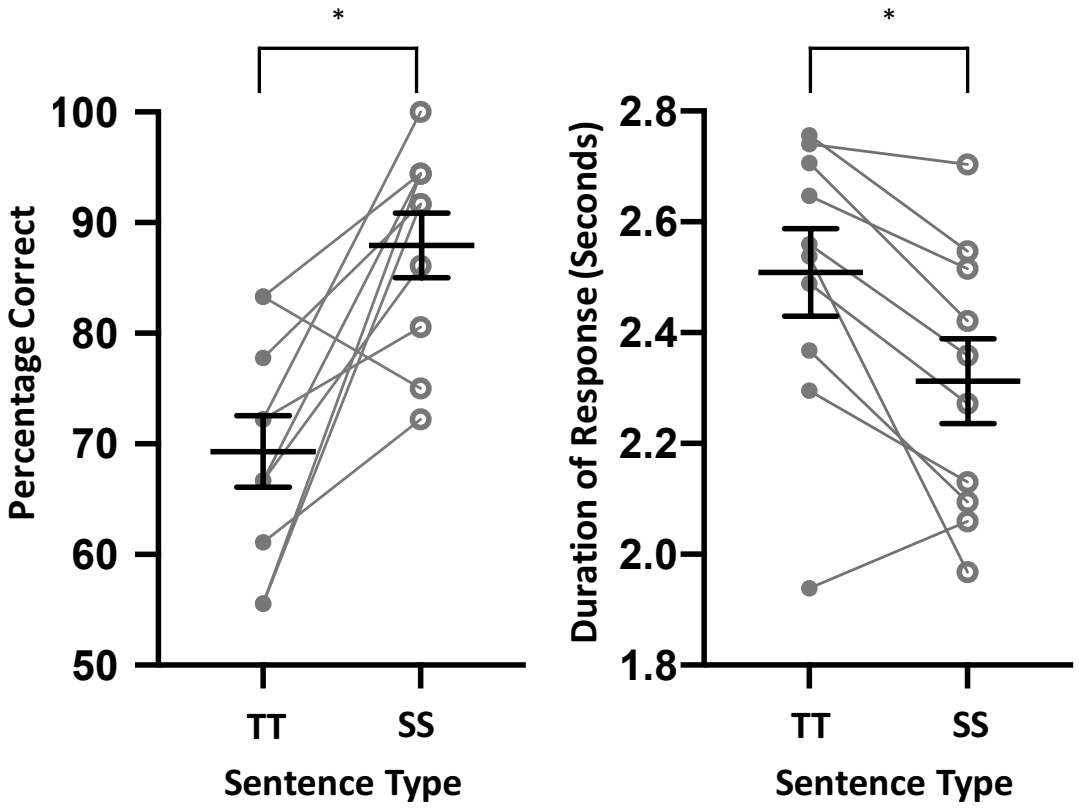


Figure 6.2 Pilot Data for Task.

Accuracy and duration of responses (seconds) for the Tongue Twister (TT) and Simple Sentence (SS) conditions. Data for individual participants are indicated with grey circles connected by lines (nine out of 10 participants made more errors and took longer to repeat the tongue twisters than the simple sentences, as predicted). Horizontal line represents mean; error bars represent 1 SEM.

As expected, participants repeated tongue twisters significantly more slowly than the simple sentences ($t(10)= 5.96$, $p < .001$). Simple sentences were repeated more accurately than complex sentences ($t(10) = 4.38$, $p<.01$).

The pilot data confirmed that the complexity of the two sentence types was successfully manipulated. Tongue twisters were repeated significantly less accurately and more slowly compared with simple sentences. Importantly, performance on both tasks indicated a range of performance with only one participant performing at ceiling in terms of accuracy on the repetition of simple sentences. For the main study, it was important to choose *a priori* one outcome variable for analysis of performance on the task in order to reduce the number of comparisons being made. Response time was therefore chosen as a dependent measure as it encompasses both reaction time and total duration of the repeated sentence and included any hesitations, self-corrections or other types of dysfluency.

Response time was measured in the same way as previously (Fiori et al., 2014), namely from the end of the stimulus presentation to the end of the participant's spoken response.

6.3.4.3 tDCS Stimulation

1mA of stimulation was delivered using a neuroConn GBH stimulator (NeuroConn GMbH, Ilmenau, Germany) via two 5 x 7cm saline-soaked electrodes. Two groups received active stimulation during which the intensity of current was ramped up slowly for 15 seconds before being held constant for 13 minutes and ramped down for 15 seconds. During the sham stimulation, the intensity of the current was ramped up slowly for 15 seconds before being held

constant for 30 seconds and ramped down for 15 seconds. These sham stimulation parameters delivered current at an ineffective dosage (Jog et al., 2016).

The anodal group received bi-hemispheric, active stimulation with the anode placed on the left hemisphere IFG/M1 and the cathode placed over the homologous area in the right hemisphere. The cathodal group received bi-hemispheric, active stimulation with the reverse electrode configuration: the cathode over left hemisphere IFG/M1 and the anode over the homologous area in the right hemisphere. To ensure blinding of the researcher, placement of the electrodes was counterbalanced for the sham group such that half were placed in the anodal condition described above and half were placed in the cathodal configuration. A simulation of current density and flow based on the equipment and parameters used in this set up is illustrated in Figure 6.3.

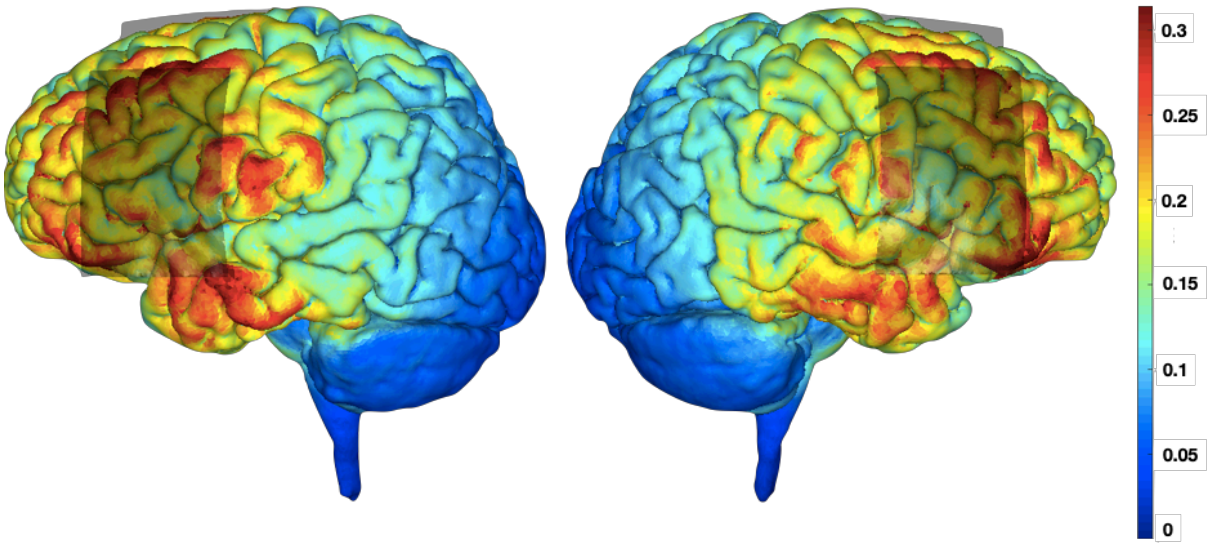


Figure 6.3 Simulated current flow

For this example, the anode is placed on the left hemisphere and the cathode on the right hemisphere. Red indicates high current density; blue indicates low current density. Simulation created using simnibs.com (Saturnino, Antunes, Stelzer, & Thielscher, 2015).

6.3.4.4 TMS and Electrophysiological recording

Single-pulse TMS was delivered using a DuoMag 200 stimulator through a 70-mm figure-eight coil. The coil was placed tangential to the skull, to induce a horizontal current flow from posterior to anterior under the junction of the two wings of the figure-eight coil. Surface electrodes (22 x 30 mm ABRO neonatal electrocardiogram electrodes) were attached to the right corner of the lower and upper lip (orbicularis oris muscle) in order to record the electrical activity of the underlying muscle. The ground electrode was attached to the forehead.

The active motor threshold was identified as the stimulation intensity needed to achieve an average MEP size that was at least 1mV peak-to-peak for 10 consecutive pulses whilst the participant maintained lip muscle contraction at 20% of their maximum. Subsequently, a train of 20 single pulses of stimulation were delivered with minimum 5-s intervals at this threshold to the left lip motor cortex to elicit the MEPs for measurement. Participants maintained the contraction of the lip muscle throughout the measurement.

For the MEP measures at post-stimulation, 20 MEPs were elicited using the same threshold (% of stimulator output) and position. BrainSight neuronavigation equipment (Rogue Research Inc, Montreal, Quebec, Canada) was used to ensure the precise area (accurate to 2 mm) is stimulated

in an identical way (position, orientation and tilt of the coil) before and after the tDCS stimulation.

The peak-to-peak amplitude of the MEPs was calculated automatically within a window of 10-40 ms after the TMS pulse. The power of the rectified EMG signal for 200 ms before the TMS pulse was used to estimate the power of the contraction for each trial. As the amount of contraction is linearly related to the size of the MEP, we used analysis of covariance for each participant to adjust the MEP size for the amount of contraction (see Watkins, Strafella, & Paus, 2003). This adjusted MEP size was used in the analyses below.

6.4 Results

The results for each group are summarised in Table 6.1.

Table 6.1 Summary of participant demographics and results.

Stimulation Group	Anodal			Cathodal			Sham		
Age *Mean (range; SD)*	22.45 (19-33; 3.63)			23.25 (19-42; 7.14)			21.25 (18-29; 2.57)		
TMS output (% max output) *Mean (SEM)*	56.6 (1.61)			57.9 (2.22)			62.2 (2.04)		
Time point (relative to tDCS)	**Pre**	**During**	**Post**	**Pre**	**During**	**Post**	**Pre**	**During**	**Post**
Tongue Twisters Response time (s) *Mean (SEM)*	3.25 (0.07)	3.14 (0.06)	3.08 (0.08)	3.22 (0.08)	3.01 (0.08)	2.92 (0.09)	3.13 (0.07)	3.00 (0.08)	2.93 (0.08)
Simple Sentences Response time (s) *Mean (SEM)*	2.89 (0.07)	2.77 (0.07)	2.79 (0.09)	2.80 (0.10)	2.63 (0.09)	2.56 (0.10)	2.75 (0.07)	2.61 (0.08)	2.62 (0.08)
Power of lip contraction (mV) *Mean (SEM)*	0.117 (0.008)	NA	0.116 (0.008)	0.142 (0.112)	NA	0.141 (0.011)	0.122 (0.010)	NA	0.120 (0.009)
MEP size (mA) *Mean (SEM)*	1.15 (0.05)	NA	1.05 (0.05)	1.16 (0.06)	NA	1.13 (0.07)	1.19 (0.07)	NA	1.14 (0.08)

SD = standard deviation, tDCS = transcranial direct current stimulation, SEM = standard error of the mean, mV = millivolts, mA = milliamps, NA = Not applicable.

The following analyses were unchanged from the pre-registration analysis plan.

6.4.1 Control Analyses

Firstly, the baseline data were analysed to confirm that the tongue twisters were repeated with longer durations compared with simple sentences (positive control) and also that there were no existing group differences at baseline. These data are plotted in Figure 6.4.

For the measure of response duration obtained pre-stimulation in the three groups, a 2 x 3 repeated measures analysis of variance (RM ANOVA), with sentence type as a within-subject factor (TT vs SS) and stimulation group as between-subject factor (anodal vs. cathodal vs. sham). There was a significant main effect of sentence type ($F(1,57) = 509.72$, $p < .001$, $d = 5.4$) due to longer response times for TT compared with SS in all three groups. There was no main effect of group ($F(2,57) < 1$) and no interaction between sentence type and group ($F(2,57) < 1$).

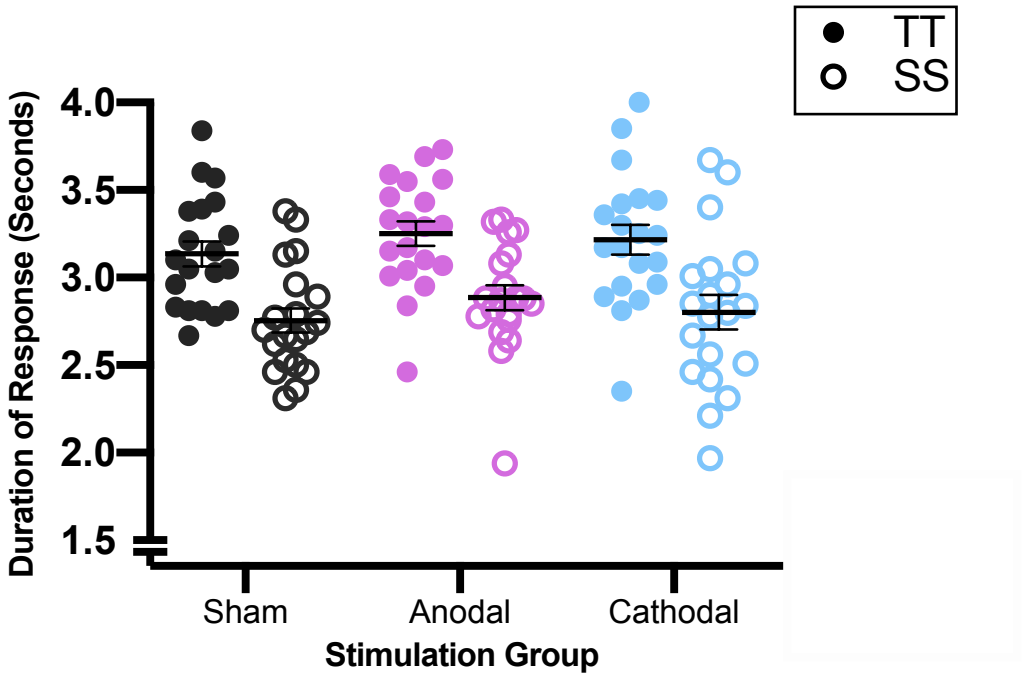


Figure 6.4 Baseline Task Performance.

Duration of responses by sentence type (TT and SS) and stimulation group. Each point represents the mean of an individual participant. The horizontal black line is the group mean, error bars represent one SEM.

6.4.2 Q1. Behavioural: Does anodal tDCS enhance learning to repeat tongue twisters in healthy young adults?

We used a 2 x 3 RM ANOVA with sentence type as a within-subject factor (TT, SS) and stimulation group as a between-subject factor (anodal, cathodal and sham) to test our hypotheses: H1A) people receiving anodal stimulation over the left hemisphere will show significantly greater improvements in sentence durations when repeating tongue twisters compared with people receiving cathodal or sham stimulation; H1B) people receiving cathodal stimulation over the left hemisphere will show significantly lower improvements in

sentence durations when repeating tongue twisters compared with the people receiving sham stimulation; and H1C) the effect of anodal stimulation on sentence durations will be greater for repetition of tongue twisters compared with repetition of simple sentences. To assess learning, we analysed the dependent measure of change in duration over time (post- minus pre-stimulation). A significant main effect of sentence type showed the magnitude of reduction in response time was significantly greater for TT than for SS ($F(1,57)=9.67$, $p=.003$, $d = 0.82$). There was no main effect of group ($F(2,57)=2.20$, $p=.120$) or interaction between group and sentence type ($F(2,57) < 1$).

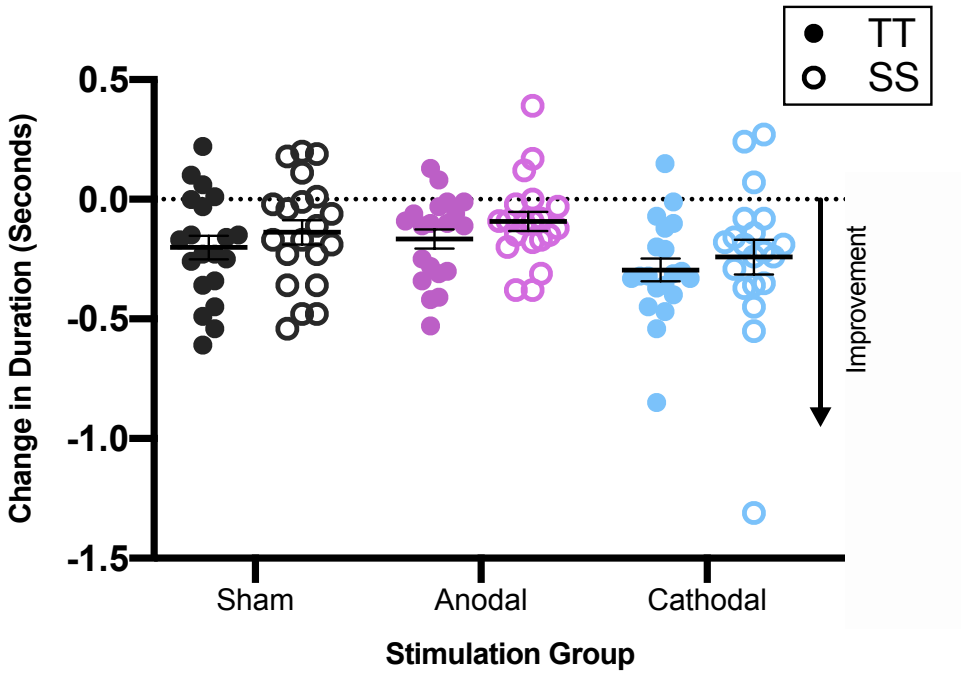


Figure 6.5 No Effect of tDCS on Learning to Repeat Tongue Twisters.

Change in duration of responses (post- minus pre- stimulation) for tongue twisters (TT) and simple sentences (SS) by stimulation group. Each point represents the mean of an individual participant. Horizontal black line shows group mean. Error bars represent SEM.

All groups showed a significant reduction in the duration of responses for repetition of sentences (i.e. one-sample t-test against no change: tongue twisters t(59) = -8.16, p <.001, d = 1.05; simple sentences t(59) = -4.80, p < .001, d = 0.62). This effect was significantly greater for the tongue twisters compared with the simple sentences, as shown in Figure 6.5. However, the lack of main effect or an interaction involving stimulation group indicates that task performance and this effect were not modulated by the anodal (or the cathodal) stimulation as predicted. Therefore, no further planned comparisons were carried out.

6.4.3 Q2. Electrophysiological: Does tDCS change excitability in the motor system underlying speech production?

To test our Hypothesis 2A (anodal tDCS over the left hemisphere will increase excitability in the speech motor system measured contralaterally compared with cathodal and sham stimulation), two t-tests compared change in MEP size (post- minus pre- stimulation) between the anodal and cathodal groups and separately between the anodal and sham groups. Directional t-tests were used as we expected an increase in MEP amplitude in the anodal group compared with the other two groups, which we expected to remain either unchanged (sham) or to decrease in amplitude (cathodal group). The change in MEP size for the anodal group was not significantly bigger than the changes for either of the other two groups (anodal vs sham: t(38) = 0.80, p = .469; anodal vs cathodal: t(38) = -0.31, p = .380).

To test our Hypothesis 2B (cathodal tDCS over the left hemisphere will decrease excitability in the speech motor system measured contra-laterally compared with sham stimulation) a single t-test was used to compared change in MEP size between cathodal and sham groups. A directional test was used as we expected a decrease in MEP amplitude in the cathodal group compared with the sham group, which we expected would not change. The change in MEP size for the cathodal group was not significantly different from that in the sham group ($t(38) = 0.29$, $p = .387$).

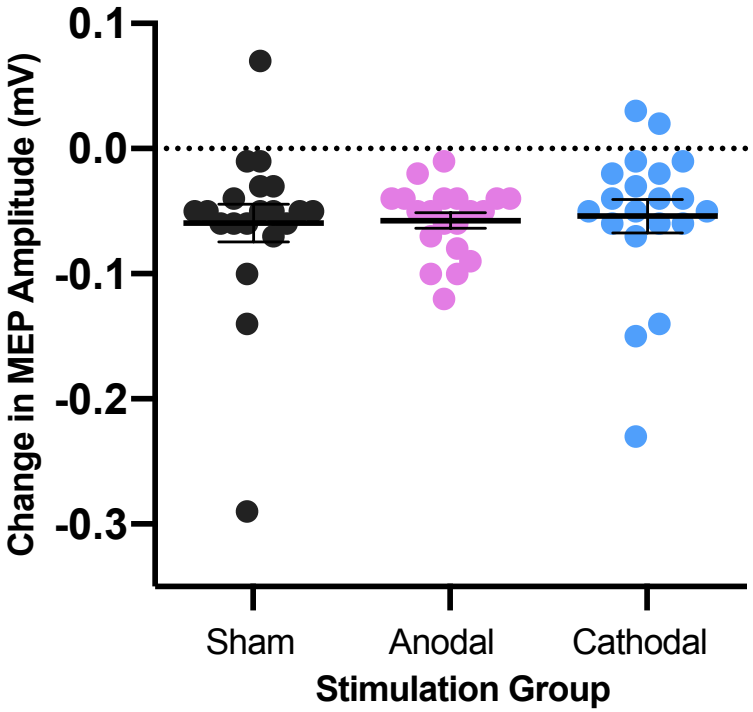


Figure 6.6 No Effect of tDCS on Excitability in the Motor System Underlying Speech Production.

Change in MEP size (post- minus pre- stimulation) by stimulation group. Each point represents the mean of an individual participant. Horizontal black line shows group mean. Error bars represent SEM. Dashed line at y=0 represents no change in MEPs.

6.4.4 Q3. Does the change in motor excitability predict learning on the behavioural task?

To test our Hypothesis 3A that change in motor excitability will correlate positively with the size of the improvement on the tongue twister task we correlated the change in MEP size with the change in duration of repetition of tongue twisters. The change in MEP size did not correlate with change in duration of repetition of tongue twisters for any of the groups (Anodal: r = -.33, p = .161; Cathodal: r = -.07, p = .757; Sham: r = -.14, p = .517). We also planned to compare the slopes of the regression lines in the three groups separately. However, because none of the correlations were significant, these comparisons were not carried out.

6.4.5 Exploratory analysis

The following analyses were not planned.

6.4.5.1 Did Task Performance Change During Stimulation?

We also tested whether tDCS affected task performance during stimulation as it did in the previous study (Fiori et al., 2014). The means and SEM for each group are shown in Table 6.1.

The change in duration of response from pre- to during-stimulation was significantly different from zero (no change) for all groups (all $p < .005$), however neither anodal nor cathodal were different from sham (anodal vs sham: t(38) = -.64, p = .529; cathodal vs sham: t(38) = 1.09, p = .284). All groups improved their performance but tDCS had no effect on this improvement.

6.4.5.2 Did the Amount of Muscle Contraction During MEP Measurements Differ Pre- and Post- tDCS?

Differences in the power of the lip muscle contraction during TMS affects MEP size. We therefore tested whether this had changed from pre- to post-tDCS in any of our groups (see Table 6.1). There were no differences between the power of contraction at pre- and post-tDCS for any of the stimulation groups (sham: $t(19) = 0.47$, $p = .645$; anodal: $t(19) = 0.859$, $p = .401$; cathodal: $t(19) = 0.29$, $p = .777$).

MEP amplitudes significantly decreased from pre- to post- stimulation for all of the groups (see Fig. 6.6) (one-sample t-test against no change, i.e. zero: $t(59) = -8.24$, $p < .001$, $d = 1.06$).

6.4.5.3 Were participants blind to whether they were receiving real or sham stimulation?

In order to test whether participants could guess if they were receiving real or sham stimulation, a 2 x 2 Chi-square test was performed. Responses from seven participants were not recorded (sham = 3, real = 4). Of the 17 people who received sham, 8 guessed it was sham and 9 that it was real stimulation; of the 36 people who received real stimulation, 11 guessed it was same and 25 that it was real. These proportions are not different to chance ($\chi^2(1, N = 53) = 1.37$, $p = .242$) indicating that participants were successfully blinded to the type of stimulation they were receiving.

6.5 Discussion

We tested whether tDCS could modulate performance on a tongue-twister task in healthy young adults. Sixty participants received either sham (n=20), or bi-hemispheric tDCS with the anode on the left (n=20) or right (n=20). Their ability to repeat sentences that were either complex (tongue twisters) or simple was tested before and after tDCS concurrent with the task. TDCS did not modulate performance on the task. Participants showed an improvement in performance and this was greater for the tongue twisters than for the simple sentences but these changes did not differ among the three groups. These results align with a recent study that also failed to replicate the original behavioural finding (Wong et al., 2019). The effect of tDCS on behaviour in neurotypical populations has been difficult to replicate (Guerra et al., 2018; Tremblay et al., 2016). This could in part reflect individual differences in the expected response to brain stimulation. Therefore, we also used TMS to elicit MEPs as a measure of motor excitability before and after the tDCS; we predicted that motor excitability would be modulated by tDCS in a polarity-specific way and that individual differences in the behavioural effects of tDCS might be explained by differences in the change in motor excitability. Our results showed no modulatory effect of tDCS on motor excitability. Participants showed a small reduction in excitability from pre- to post-stimulation but this did not differ among the three groups.

These results contrast with those previously reported (Fiori et al., 2014). There are a number of differences between study protocols that might explain the failure to replicate. Firstly, we

changed the electrode montage from uni-hemispheric to bi-hemispheric and placed them slightly more posteriorly in order to ensure stimulation of the lip representation of M1. It is unlikely that the slight difference in position of large electrodes compared with the original study reduced the effectiveness of tDCS coupled with the task as indicated by our modelling of the current flow for our study (see Figure 6.3). In addition, bi-hemispheric montages are at least as effective as uni-hemispheric ones (Fiori et al., 2017; Meinzer et al., 2014; Prichard, Weiller, Fritsch, & Reis, 2014) or can even improve the effects on task performance (Drummond, Hayduk-Costa, Leguerrier, & Carlsen, 2017; Vines et al., 2008; Waters, Wiestler, & Diedrichsen, 2017). Secondly, we reduced the current amplitude from 2mA to 1mA and the duration of stimulation from 20 minutes to 13 minutes. In our experience and that of other reports, blinding of the participant is not achieved at 2mA due to the increased somatosensory experiences, e.g. tingling and itching under the electrodes (O'Connell et al., 2012). Our debriefing indicated that participants were blind to stimulation type at 1mA. Previous reports (Kidgell et al., 2013) and our own experience (Chesters, 2016) suggests that increasing stimulation intensity beyond 1mA does not increase the effectiveness of anodal stimulation over the ventral motor cortex. In addition, reducing the duration of stimulation is unlikely to explain our null results as numerous reports of tDCS applied to the motor cortex in healthy humans show behavioural modulation with stimulation durations of between 10 and 16 minutes (Lametti et al., 2018; Lang, Nitsche, Sommer, Tergau, & Paulus, 2003; Monte-Silva et al., 2013; Nitsche et al., 2003; Stagg & Nitsche, 2011). In sum, we believe the changes to the stimulation protocol described above are unlikely explanations for our failure to detect a modulatory effect on task performance in this study. We turn next to the changes we made to the behavioural protocol.

Our study used different stimuli for the task and introduced a control task (repetition of simple sentences). Necessarily, the language of the sentences was changed from Italian to English. If the speech motor effect is generalisable across languages, this would not explain the difference in results. Our tongue twisters were novel rather than well-known (as in Fiori et al., 2014) and shorter than those used previously; the mean response time for tongue twisters at baseline in our study was 3.2 seconds, whereas it was ~4.5 seconds in the previous study (Fiori et al., 2014). Our study may have been less sensitive to changes in behaviour between stimulation groups because of these differences in stimuli.

The most important difference between the two studies was the age of the participants. Both studies included neurotypical participants but those in (Fiori et al., 2014) were considerably older (mean = 57 years; SD = 11) than those in the current study (mean = 22.3 years, SD = 4.8). In our view, this age difference is the most plausible explanation for the different findings between the two studies. For example, in a previous study, TDCS with a concurrent visuomotor adaptation task significantly improved performance of healthy older adults to the level of that seen in younger adults without stimulation (Panouillères, Joundi, Brittain, & Jenkinson, 2015) suggesting that age-related declines in task performance can be reversed using tDCS. Taken together, the reduction in the sentence length for our study and our focus on younger healthy adults may have reduced our sensitivity to the modulatory effects of tDCS (Fiori et al., 2017).

In the current study, we added electrophysiological measurements of motor excitability to assess tDCS changes using TMS-induced MEPs. Our aim was to explain individual

differences in the anticipated modulatory effects of tDCS on task performance by variability in the modulatory effects of tDCS on motor excitability. In some respects, we succeeded, in that the failure to find an effect of tDCS on task performance was mirrored by a lack of effect of tDCS on motor excitability. Nevertheless, this result was unexpected given previous established results that tDCS modulates MEP size in a polarity-specific way (Nitsche & Paulus, 2000). It is important to note, however, that these modulatory effects were found in studies that did not involve a concurrent task (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). A previous report found that anodal tDCS (1mA, 20 minutes) applied without a concurrent task increased MEP size as expected but when the stimulation was applied in combination with a digit-sequence task, MEP size was not modulated even though task performance measurably improved (Amadi et al., 2015). One explanation of these results is that during task performance the brain alters its excitability to counteract the effects of tDCS. Such homeostatic regulation would therefore abolish the measurable effects of tDCS on motor excitability. This suggestion could be important in explaining the variable results within the tDCS literature and aid optimisation of tDCS protocols.

It is possible that tDCS is most effective when the area of cortex being stimulated functions atypically. For example, left ventral premotor cortex is known to be underactive during speaking in people who stutter compared with controls (Watkins et al., 2008) and anodal tDCS over this area improved fluency in people who stutter compared with sham stimulation (Chesters, Möttönen, & Watkins, 2018). Similarly, tDCS led to modulated performance on a digit sequence task in the non-dominant, but not the dominant hand of neurotypical adults (Boggio et al., 2006). In our opinion, the negative results for both task and motor excitability in the current study are best explained by the fact that our healthy young adults function

optimally, which renders modulation by tDCS ineffective. Note, that this is not simply due to a behavioural ceiling effect as there was room for improvement on task performance both in terms of latency and accuracy, which would have affected response time. Furthermore, the cathodal stimulation was expected to lower performance and was also ineffective.

In summary, our study failed to demonstrate the previously reported polarity-specific modulatory effects of tDCS on speech motor control in a typical population. Our study had a sample size double that of the previous study and was sufficiently powered to detect a similarly sized effect. The factor of participant age and how this interacts with brain function is the most likely explanation for this failure to detect an effect should one exist. The alternative explanation is that the effect cannot be replicated but the changes we made to the protocol and the population difference in age precludes such a firm conclusion. The lack of modulation by tDCS on motor excitability is consistent with the lack of effect on behaviour but we believe this is better explained by homeostatic regulation of cortical excitability that may occur during task performed concurrently with tDCS in the typically functioning brain.

7 General Discussion

7.1 Summary of Findings

The overarching aim of this thesis was to further our understanding of speech motor control in people who stutter (PWS) and people who are typically fluent (PWTF). To do this, I used a multi-modal approach including vocal tract MRI, functional MRI during task and brain stimulation. These methods allowed me to explore speech motor control from the brain's control of speech to the movement of the articulators.

7.1.1 Measuring articulation

First, I conducted a systematic review of previous studies of articulation in PWS. I concluded that the strongest evidence was for greater variability in the speech movements of PWS compared with PWTF. Evidence for other kinematic differences, such as the muscular effort involved in speech, was limited by the small number of studies and hampered by small samples and methodological issues. I then wanted to test whether the novel method of vocal tract MRI was feasible to capture the variability of articulator movement in PWS and PWTF. I designed a study to compare vocal tract imaging with previous methods that measured lip movements (e.g. using infra-red light emitting diodes; Smith, Sadagopan, Walsh, & Weber-Fox, 2010) and extend measurements to other articulators within the vocal tract; the tongue and the velum. The results showed convincing evidence for greater variability in the speech of PWS compared with PWTF, even during fluent utterances of simple nonwords. Movements in PWS were more variable than PWTF in all articulators measured. This study is the first to

report the use vocal tract MRI with PWS and provides proof-of-principle evidence for the sensitivity of this method to subtle speech motor differences in PWS.

7.1.2 Measuring brain differences in speech motor control.

I then looked at speech motor control at the brain level. I used the Stop-Signal task that was previously used to investigate inhibitory motor control of movements (Xue, Aron & Poldrack, 2008). The behavioural results showed that PWS were slower to initiate a response on 'go' trials (that required a button press in response to a visual stimuli), but that the time it took to inhibit a response was not different between groups. Accordingly, the groups differed in the brain activity during 'go' responses: PWS showed overactivation in key areas of the motor-control network. In contrast, there was only qualitative overactivation during stop trials in PWS, but no significant difference between the groups. Specifically, a key area implicated in the cognitive control of movements, the right inferior frontal gyrus (IFG) was overactive in PWS during 'go' and 'stop' trials, whereas controls only activated this area during 'stop' trials. I concluded that overall, this provided support for the overactive inhibition hypothesis, which suggests that PWS are in a general state of heightened inhibition compared to PWTF.

7.1.3 Modulating Speech Motor Control

Finally, I wanted to investigate whether we could use what we know about the brain's control of articulation to modulate speech motor control. The PWS that contributed data to the vocal-tract and task functional MRI are part of an ongoing RCT. The data presented here were obtained at baseline in all participants prior to an intervention that aims to replicate a previous

finding from our lab that non-invasive brain stimulation (specifically tDCS) improves speech fluency in PWS (Chesters et al., 2018). I wanted to evaluate whether tDCS could also be used to improve articulation in PWTF as well. I aimed to replicate a previous finding that showed tDCS modulated performance on a complex articulation task (repetition of tongue twisters). This was a conceptual replication as we changed some stimulation parameters of the study based on recent optimization studies. My results revealed that tDCS did not modulate behaviour. In addition, I used transcranial magnetic stimulation (TMS) to measure cortical excitability of the motor cortex before and after tDCS. As with the behavioural result, tDCS did not modulate cortical excitability. This failure to replicate raised interesting questions about how areas of cortex that are typically functioning, compared with atypically functioning, may respond to tDCS. Specifically, we need to consider whether factors affecting performance such as normal ageing or a fluency disorder might be necessary to demonstrate the beneficial effects of stimulation on tasks.

7.2 Considerations and Future Work

The studies contributing to this thesis raised a number of interesting issues. In the following discussion, I consider these issues in the context of ideas for future work.

7.2.1 Optimizing analyses for vtMRI

Chapter 4 provided the first evidence of articulation differences between PWS and PWTF using vocal tract MRI. I chose to measure the variability of three articulators; the lips, tongue

and velum. However, vocal tract MRI provides a very rich data set, which offers more possibilities for understanding articulatory control in typical and atypical speech. For example, the grid-based segmentation analysis used in chapter 4 separates the vocal tract into ~70 gridlines. My analyses chose just three of these gridlines, one for each of the articulators measured. However, with this large amount of data comes a multiple comparisons problem. For example, linear mixed models, as used in chapter 4, would not be suitable for this number of variables. Instead, data reduction techniques may be more optimal for capturing modes of variation across the entire vocal tract. Data reduction techniques, such as principal components analysis (PCA), aim to reduce a large number of measurements into the smallest number of components that could together account for a substantial amount of variance in the data. In the case of our analysis of vtMRI, each component would represent variance from regions of the vocal tract based on meaurements from groups of grid lines. From this, we could examine which articulators contribute the most variability, and if these components differ between PWS and PWTF.

Rather than going very broad scale, as with PCA, an alternative approach would be to look more closely at the relationship between each of the articulators on a trial-by-trial basis. This approach can be used to measure the precise co-ordination and timing between the articulators. For example, we could ask whether the timing of movement between two or more articulators is stable, or more variable in PWS than PWTF.

7.2.2 An overactive inhibition explanation for developmental stuttering?

Chapter 5 used fMRI to test the hypothesis that developmental stuttering is, in part, caused by an overactive neural inhibition response (Neef, Anwander, et al., 2018). We showed that PWS

overactivated key areas of the inhibition network, including the IFG, SMA and basal ganglia, during 'go' responses. I concluded that this might be because PWS are in a constant state of heightened inhibition. However, there were no significant differences between the brain activity of PWS and PWTF during stopping responses. This may be because the activity that we ascribe to the 'inhibition network' is in fact not caused by differences in inhibitory control. Or, it may be that our design and analysis were not sensitive enough to detect differences between groups.

Our fMRI study was limited in the number of stopping trials that could be captured in PWS (24 compared with 144 go trials) due to the nature of the stop signal task and time constraints. Regardless, using fMRI can only tell us about the neural correlates associated with the behaviour (initiating and inhibiting a manual response). This work takes us closer to understanding the relationship between inhibition and stuttering, however two questions remain: 1) is the activity seen specific to inhibition and 2) if this activity does represent overactivity in the inhibition network, is a cause or a consequence of stuttering? TMS can help to answer these questions. TMS can be used to temporarily reduce the functioning of a targeted area of cortex ('virtual lesion' design). During this temporary time window, researchers can assess the differences in behaviour as a result of the stimulation allowing us to see if that area of cortex contributes to the behaviour. Previous work has used TMS to investigate inhibitory control of non-speech movements in a typical population (e.g. Chambers et al., 2007). In this work, rTMS was applied to the left and right IFG in turn, before participants performed the stop signal task. Stimulation of the right IFG impaired stop-signal inhibition, but stimulation to the left IFG had no effect on task performance (Chambers et al., 2007). This implicates the right IFG in the control of inhibition. A similar methodological

framework might be used to understand the causal role of brain regions involved in 1) inhibition and 2) stuttering.

The striking pattern of overactivity in the PWS on 'go' trials as well as for the other trials in the task was surprising. Although overactivity in stuttering populations has been noted previously on speech tasks, the pattern is not as widespread as seen here and there are often areas of underactivity observed also. In a recent study from our lab, when only fluent utterances were analysed in PWS, there were no areas of overactivity – rather the pattern was one of underactivity (Connally et al., 2018). Overactivity was observed when dysfluent utterances were compared with fluent utterances within the same participants. The pattern of significant activation on 'go' trials in the current study was also surprising because the task was a simple button press made with the index finger of the right hand. Controls activated the predicted areas associated with simple movements such as this. The same model of the HRF response was convolved with the event-related design for all participants on the 'go' trials but it is possible that our assumption regarding the timing of the HRF is wrong in the PWS group. This factor would not significantly affect the previous studies, which used block designs or sparse sampling in which the HRF is typically not modelled. This may be true for PWS compared to PWTF as a group, or even between different brain regions. For example, one study isolated the time course of rIFG activation during speech in PWS and PWTF (Neef et al., 2016). Compared with other left hemisphere regions activated by speaking (including the IFG and temporal areas) the right IFG showed delayed peak activations, corresponding to the end of utterances, for both PWS and PWTF, with stronger peaks in PWS. Understanding HRF response variation within and between groups will be important for future event-related designs.

7.2.3 Population differences in response to tDCS

Previous work shows that there is also a large amount of variability in how brains respond to tDCS (Horvath, Forte, & Carter, 2015; Wiethoff et al., 2014). The aims of tDCS studies are to understand the contribution of an area of brain to a particular function and to test whether tDCS can improve the efficacy of behavioural therapies. If we are to reach these aims, we must understand individual variation in the response to tDCS. I attempted to see whether the cortical response to tDCS (operationalized by the size of the motor evoked potential) could explain individual responsiveness to tDCS. The results show that this was not possible as the cortical excitability was not modulated by the tDCS. Instead, I concluded that the discrepancy between my findings and the previous work (Fiori et al., 2014) was best explained by their use of older adults compared with our younger adults. For example, in a previous study, tDCS with a concurrent visuomotor adaptation task significantly improved performance of healthy older adults to the level of that seen in younger adults without stimulation (Panouillères et al., 2015) suggesting that age-related declines in task performance can be reversed using tDCS. It is therefore possible that tDCS is most effective when the area of cortex being stimulated functions atypically. In the case of speech, for example, left ventral premotor cortex is known to be underactive during speaking in people who stutter compared with controls (Belyk et al., 2015; Watkins et al., 2008) and anodal tDCS over this area improved fluency in people who stutter compared with sham stimulation (Chesters et al., 2018). Similarly, tDCS led to modulated performance on a digit sequence task in the non-dominant, but not the dominant hand of neurotypical adults (Boggio et al., 2006). I believe that the negative results in the tongue twister study (chapter 6) are best explained by the fact that our healthy young adults function optimally, which renders modulation by tDCS ineffective.

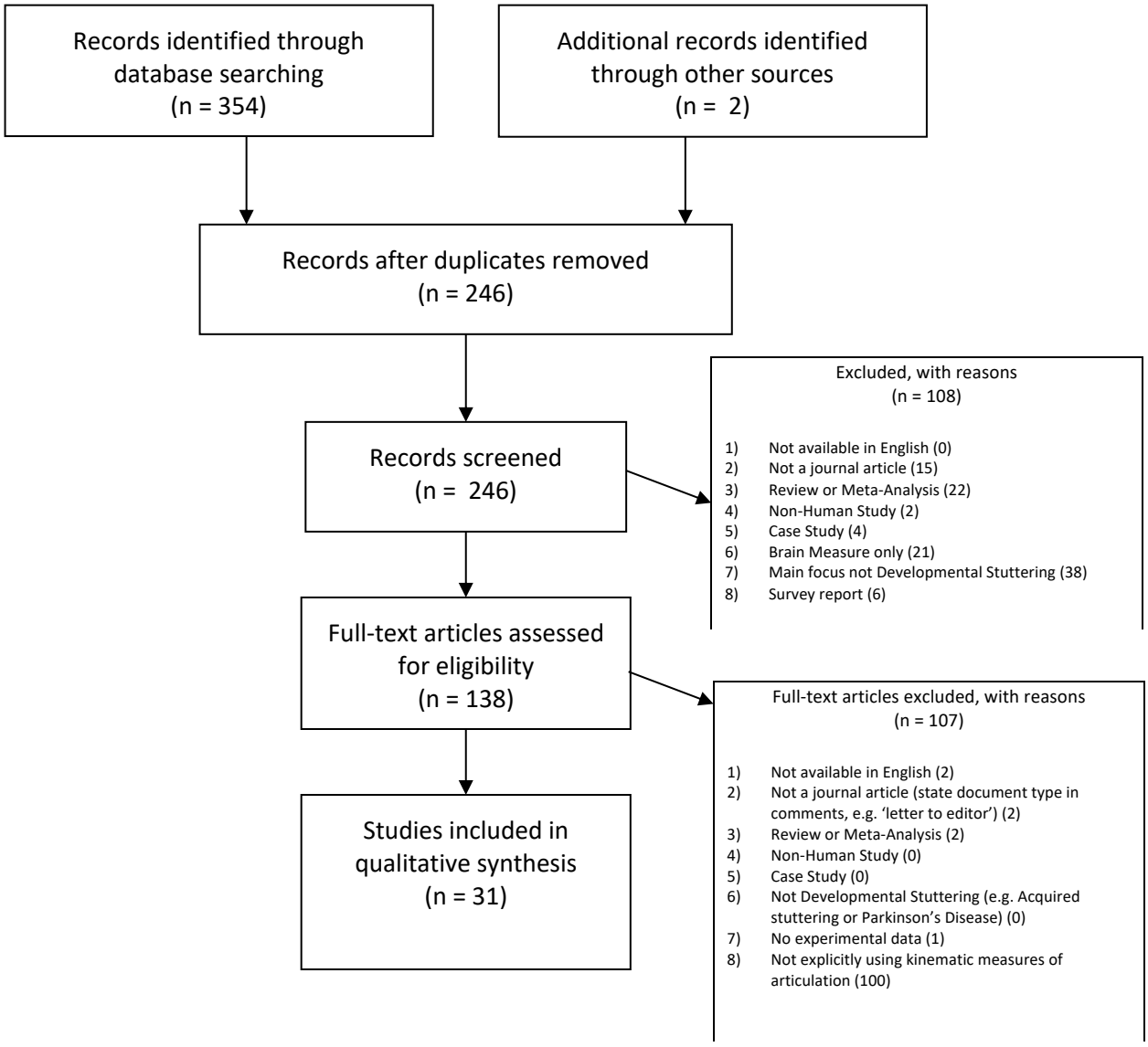
Modelling how cells will respond to tDCS, based on the relationship between their anatomical position and the current density can help to predict individual responses to tDCS (Bikson & Rahman, 2013; Jog et al., 2016). However, my conclusions above suggest that factoring in how the area of cortex functions will also be important. It would be predicted that areas of cortex that function atypically would respond differently to areas that are functioning optimally. Combining tDCS with neuroimaging could address this hypothesis. In previous work, tDCS concurrent with fMRI revealed changes in activation and connectivity within the naming network, associated with anodal-TDCS over left IFG (Holland et al., 2011; Holland et al., 2016). This principle could be applied to describe individual differences within typical populations and also between typical and atypical populations.

7.3 Conclusions

The studies in this thesis show that PWS have differences in speech motor control at the articulation and brain levels. The use of vtMRI in chapter 4 is the first demonstration of how this novel technique can be used to understand articulator control in PWS. In addition, chapter 5, I find some preliminary support for the idea that PWS have overactivity in the inhibition network. Finally, I showed that tDCS does not modulate performance on a complex articulation task, nor does it modulate the cortex in a young and healthy population. In doing so, this thesis raises interesting questions as to how tDCS can be most optimally applied and for which individuals it may be most effective.

Appendices

Appendix 1: Prisma Flow Diagram



Appendix 2: Summary of Studies in Systematic Review (Chapter 3)

Citation	Title	Method	Method description	Participants	Measured variable(s)	Task	Main Finding(s)	Point
(Ambrose et al., 2015)	Relation of motor, linguistic and temperament factors in epidemiologic subtypes of persistent and recovered stuttering: Initial findings	Strain-gauge transducer	7 time-points taken over 4 years after the onset of stuttering.	2–4-year-old CWS defined as persistent or recovered. Range of 1-14 children in each group for each visit. 40 age and gender matched normally-fluent controls. Range of 6 – 11 participants for each time point.	Jaw displacement STI	Sentence repetition. 'papa' and 'buy papa a puppy' 15 times each	Recovered participants had significantly greater variability indexes (STI) than fluent controls at visit 5. Appears to be driven by controls becoming less variable. No significant differences between controls and persistent stutterers at any time point. However, Persistent and recovered children who stutter had greater STI scores than controls for each time point (Not significant).	No support for differences in variability of jaw movements between persistent/recovered children who stutter. Trend towards CWS having greater STI scores than fluent controls (N.S)
(Andrade, Queiróz, & Sassi, 2010)	Electromyography and diadochokinesia--a study with fluent and stuttering children	EMG	EMG electrodes placed on both sides of inferior OO muscle	19 Children "school age" children who stutter 31 fluent age-matched controls	EMG amplitude	DDK task - sequence repetition "pa-pa-pa", alternating repetition "pa-ta-ka"	CWS had lower EMG amplitude than fluent controls during sequence repetition.	CWS do not show greater muscle excitation of the lips whilst performing sequence repetition.
(Choo et al., 2010)	Different lip asymmetry in adults who stutter: electromyographic evidence during speech and non-speech	EMG	EMG electrodes placed on 4 quadrants; lateralised superior and inferior OO muscle.	5 AWS (mean age = 26 years; SSI score "mild" - "moderate") 5 age-matched fluent controls.	Peak EMG amplitude for each of the tasks.	Single word picture naming tasks (4 /f/ and 4 /p/ initial sounds). 5 repetitions of each word. Sentence reading repetition task (first line of grandfather passage "you wished to know all about my grandfather"). 5 repetitions at normal speaking rate. Lip pursing task. Lips pursed to mimic "pool" 20 times.	For AS, the highest EMG amplitude was in the region of the left lower lip, which is indicative of greater right hemisphere participation ANS the right lower lip displayed the highest EMG amplitude, suggesting greater left hemisphere participation AS showed greater asynchronous lip activity than ANS for all tasks	Suggests reversed lateralization for speech and non-speech processing and reduced coordination of speech musculature in AS.

(Daliri, Prokopenko, & Max, 2013)	Afferent and efferent aspects of mandibular sensorimotor control in adults who stutter	Jaw Movement Robot	Measured jaw movements and participant perception of jaw movement	11 AWS (mean age = 28.9, range = 20- 49 years; 9 males 2 females; SSI score "very mild- very severe") 11 controls (mean age = 29.1, range = 22-47 years; 9 males, 2 females)	See tasks	1) Participants make smallest movement possible given visual feedback. 2) Passive jaw movement and participants report first detection 3) Accuracy of jaw movements towards memorized kinematic targets 4) Report jaw position after passive jaw movements	No statistically significant differences between groups for any of the tasks. Statistically significant correlation between mandibular size and performance in the active and passive near-threshold tasks for PWS but not controls.	Stuttering individuals' performance varied with anatomical properties Stuttering participants generate and perceive movements on the basis of less accurate internal models of the involved neuromechanical systems
(De Andrade et al., 2008)	Persistent Developmental Stuttering As A Cortical-Subcortical Dysfunction Evidence from muscle activation	EMG	Measurements from one EMG electrode, central inferior OO at rest	11 PWS. (mean age = 25.1 years; 4 females, 7 males; SSI score < "very mild"). 11 controls (mean age = 31.5 years; 4 females, 7 males)	EMG amplitude (normalised by % of highest amplitude for each participant)	1) Rest – participant stayed at rest for one minute after which EMG signal was recorded for 5 seconds. 2) Speech reaction time – each participant was instructed to repeat the phrase "Barco na água"3 (boat on water) after they heard a beep. Only audibly fluent utterances were included.	PWS had higher EMG amplitude during rest than PWNS but no differences found in speech reaction time or EMG amplitude during speech. Significant correlation between speech reaction time and muscle activity during speech for PWS but not PWNS. The slower the reaction time, the larger the amplitude.	PWS exhibit anomalies in speech motor output during fluent speech and rest
(de Felício et al., 2007)	Comparison of upper and lower lip muscle activity between stutterers and fluent speakers	EMG	Electrodes placed centrally on upper and lower lips	10 PWS (mean age = 13.4, range = 10-18 years). 10 PWNS matched gender and age	Mean amplitude over 15 seconds. Signals of lip pursing gestures were used to normalize all the other acquired signals.	Resting state: pre- and post-task. Lip gestures: pursing, compression retraction, lateralisation (united lip movement to the left or right, not separate muscles) Speech: Repetitions of 'pai' and repetitions of sentences containing 'pai and 'batata'	PWS had smaller EMG amplitude in the upper lip for 'rest post-exercises' compared with controls. For the tasks, PWS had smaller EMG amplitude of the upper lip compared with controls for the lip lateralisation task only. There were no significant differences in EMG amplitude for lower lip.	PWS do not show increased EMG amplitude during rest or speech, contrary to hypotheses. In two out of six variables, PWS showed a decrease in the upper lip, only.

(Frisch et al., 2016)	Anticipatory coarticulation and stability of speech in typically fluent speakers and people who stutter	Ultrasound	Ultrasound of the tongue position during a velar stop. Spline applied semi-automatically to mid-sagittal tongue trace.	23 PWS (19 males, 4 females) 23 controls (12 males, 11 females). Age range across all participants = 18 – 29 years. Stuttering was self-reported and confirmed by author using SSI.	The average distance between curves (tongue position) within the same vowel context (variability over repeated utterances)	Eighteen monosyllabic (CVC or CV) words embedded in a carrier phrase The stimuli consisted of the initial velar stop /k/ followed by one of nine Standard American English vowels Each stimulus phrase was produced three times in a row, for a total of 6 productions of /k/ for each vowel context across the experiment.	No difference in co-articulatory anticipation between groups. PWS were more variable within each vowel context. Co-articulation and variability correlated for PWS but not PWNS. Many were within the normal range, with 7 PWS outside a 2SD range for variability.	Articulatory maturation in young adults who stutter is, on average, no different from typical young adults, but some young adults who stutter could be viewed as having less stably activated articulatory sub-systems.
Heyde, Scobbie, Lickley, Drake, (2016)	How fluent is the fluent speech of people who stutter? A new approach to measuring kinematics with ultrasound	Ultrasound	Ultrasound of the tongue position during a velar stop. Spline applied semi-automatically to the ultrasound pictures.	3 PWS (age bands = 25-60; 1 female, 2 males; SSI “mild – severe”) 3 PWNS (age bands = 25-60; 1 female, 2 male) Matched for age/gender and education	Onset and offset movement durations Maximum velocities for onset and offset movements	Combinations of CV syllables with a voiceless velar stop (/k/) followed by a corner vowel (/i/ or /ɑ/) or schwa (/ə/). All preceded by a schwa (/ə/). i.e. produce the pseudo-noun phrases ‘a kaa’, ‘a kuh’, ‘a kee’	Onset and offset durations and peak velocities were not different between PWS and controls. Descriptive difference between peak velocities at offset.	No statistical differences in duration or velocity of movements between PWS and controls. Lack of difference may be due to small sample size.

(Howell et al., 2009)	Comparison of acoustic and kinematic approaches to measuring utterance-level speech variability	Acoustic Strain Gauge transducers	Strain gauge transducers measured along superior-inferior plane Amplitude envelope of acoustic signal	13 PWS (mean age = 14 years 3 months; 2 females, 11 males; SSI score = "very mild – severe" 12 controls (mean age = 16 years 11 months; 7 females, 5 males)	L-STI = train guage transducers E-STI: average of the sum of amplitude values within each ms frame STI	Produce "Buy Bobby a Puppy" 20 times and normal speaking rate 10 fluent utterances used for analysis. Non-fluent utterances not included.	Lip-STI correlated significantly with Amplitude Envelope-STI STI decreased with age for both E-STI and E-STI. Overall, PWS had higher STI scores (greater variability) than controls.	Acoustic-STI was comparable to Lip-STI but was not perfectly the same. Evidence for a general system (from all articulators) that contributes to variability. This is comparable to the variability of an individual articulator (e.g lip).
(Jackson et al., 2016)	The Impact of Social-Cognitive Stress on Speech Variability, Determinism, and Stability in Adults Who Do and Do Not Stutter	IREDs	IREDs on middle of upper and lower lip	Twenty AWS (mean age = 27.4, range = 18 – 49 years; six females, 14 males; SSI scores = 8 – 43) 21 fluent controls (mean age = 25.3, range = 19 – 30; years seven females, 14 males)	STI (see Smith et al., 2010) RQA (Determinism and Stability; Detailed methods available in Jackson, 2015) Duration Social-cognitive stress with and without observers in the room	4 sentences repeated 20 times each. First 10 fluent utterances used for analysis Sentences varied in length ("buy bobby a puppy" vs "One two three four buy bobby a puppy five sex seven") and syntactical complexity (e.g. "Sarah wants to buy bobby a puppy but there's none in the shop")	PWS had higher STI scores than PWS and PWS become less variable when there are observers in the room. Split into people who were more anxious during audience than non-audience condition ("shifters"). Those who "shifted" also shifted to have more deterministic/stable speech than those who did not. The AWS exhibited longer utterance durations than AWNS across all conditions and sentences There was a positive correlation between duration and STI measure	AWS seem to adopt a more restrictive, less flexible speaking approach in response to social–cognitive stress, which is presumably a strategy for maintaining observably fluent speech.

(Van Lieshout et al., 2014)	The impact of threat and cognitive stress on speech motor control in people who stutter.	EMA	EMA of upper and lower lips.	Ten PWS (mean age = 30.6, range 22–48 years; 7 males, 3 females; SSI = "very mild" to "moderate") Ten controls (mean age = 28.4, range = 20–47 years; 7 males, 3 females).	Movement range Movement duration Cyclic Spatio-Temporal index (cSTI)	Emotional Stoop Task: Threat words specific to stuttering. Classic Stroop Task	PWS were slower to react and made smaller upper lip movements when performing the emotional stroop and classic stroop tasks compared with fluent controls. Upper and Lower lip movements were significantly more out of phase with each other compared to fluent controls. No significant differences for interactions with emotional context or nine other contrasts including reaction time, duration, cSTI.	Some evidence for specific group differences for specific threat words Many contrasts showed no differences between groups.
(Loucks & De Nil, 2006a)	Anomalous sensorimotor integration in adults who stutter: A tendon vibration study	Tendon Vibration Strain Gauge	Applied vibration to the masseter tendon. Measured jaw movement with strain gauge	Nine adult males who stutter (age range: 24–43 years; SSI range = "very mild" – "moderate") Twelve adult males who do not stutter (age range = 20–40 years)	Peak displacement Peak velocity of the movement Total variability of movement amplitude	Jaw movements at three phases: rest – target – rest.	Tendon vibration led to smaller movements, and reduced peak velocity in both groups compared to no vibration. No significant group or interaction effects. PWS reduced their movement less than people who stutter but was n.s	PWS and fluent controls reacted in a similar way to the tendon vibration.
(Loucks & De Nil, 2012)	Oral sensorimotor integration in adults who stutter	Tendon Vibration Strain-gauge	Applied vibration to the masseter tendon. Measured jaw movement with strain gauge	Ten male PWS (age range = 19 – 42 years; SSI range = "mild" – "severe") Ten male fluent controls (age range = 20 – 40 years)	Accuracy and variability of jaw opening amplitude relative to target amplitude. Peak velocity, duration and RT of the movement.	Jaw movement at three phases: Rest – target (18mm) – rest. 4 conditions: with and without visual feedback combined with 'self-selected reaction time' and 'as rapid as possible' RT conditions.	Both groups were more accurate and less variable in the visual feedback condition compared to the no-feedback condition. Combined, PWS were less accurate and more variable than controls. Observation that tendon vibration led to smaller movements, in both groups compared to no vibration (n.s).	Fluent Controls have greater sensitivity to masseter vibration then PWS.

							For fluent controls, the amount of error and variability was correlated with the undershoot of the movement. For PWS, the amount of error and variability was not significantly correlated with the undershoot of the movement, although a trend exists.	
(Loucks & De Nil, 2006b)	Oral kinesthetic deficit in adults who stutter: a target-accuracy study	Strain-gauge	Strain-gauge measured jaw movement	17 male PWS (age range = 18 – 43 years; SSI range = "very mild" – "very severe"). 15 fluent controls (age range = 20 – 40 years; 2 female, 13 males)	Accuracy and variability of jaw opening amplitude relative to target amplitude. Peak velocity, duration and RT of the movement.	Jaw movement at three phases: Rest – Target (6mm) – Rest. 4 conditions: with and without visual feedback combined with 'self-selected reaction time' and 'as rapid as possible' RT conditions.	Both groups were more accurate and less variable in the visual feedback condition compared to the no-feedback condition. Both groups made less accurate and more variable movements in the reaction time condition. Combined, PWS were less accurate and more variable than controls. PWS performed disproportionately worse in the non-feedback condition and fast RT conditions compared to the feedback and self-selected RT conditions, respectively. No differences were found between groups for RT and duration of the movement. Peak velocity was significantly larger than then control group.	PWS show an oral-kinaesthetic deficiency.
(Loucks et al., 2007)	Jaw-phonatory coordination in chronic developmental stuttering	strain-gauge electroglottography (EGG)	Strain-gauge measured jaw movement EGG to measure adduction and abduction of the vocal folds during phonation.	11 male PWS (age range = 20-40; SSI range "very mild" – "moderate"). 11 male controls (age range = 20 – 40)	Accuracy and variability of jaw opening amplitude at phonation onset relative to target amplitude.	Jaw movements at three phases: rest – target – rest whilst producing a vowel sound. Target distance varied (6mm, 15mm) and speed varied (prolonged, quick) Feedback of accuracy provided.	For both near and far targets combined, PWS performed less accurate movements and were more variable in their movements than fluent controls. No further group/interaction effects for speed or duration of movements.	PWS show a proprioceptive deficit compared with fluent controls

(MacPherson & Smith, 2013)	Influences of sentence length and syntactic complexity on the speech motor control of children who stutter	IREDs	IREDs placed on upper lip and lower lip at midline	16 Children who stutter (age range 4-6 years; 12 boys, 4 girls) 16 fluent controls (age range: 4 – 6 years)	Lip aperture STI (See Smith et al., 2010) Movement duration	Four declarative sentences that varied in length (6-9 words) and syntactic complexity (with, or without subject-relative clause) 10 error-free and fluent productions with normal prosody for each sentence (minimum of 6 repetitions from minority of participants)	Overall trend for PWS producing more variable movements than controls (n.s.) Variability of movements increased with length of the sentence for both groups. CWS were more variable than controls for simple, but not complex sentences. Variability increased with sentence complexity for controls. Variability for PWS did not change. Movement duration was longer for complex sentences compared to length-matched simple sentences for both groups.	CWS produce more variable movements than controls for simple movements. Variability index scores increased with phonological complexity of the sentences for controls only. CWS remained stable but high. Considerable individual differences in performance.
(Max & Gracco, 2005)	Coordination of oral and laryngeal movements in the perceptually fluent speech of adults who stutter	Strain-gauge EGG	Lip aperture (Upper lip - Lower lip plus jaw) Superior-inferior movements Vocal fold vibrations	Ten AWS (mean age = 34.3, range = 27 – 45 years; 7 males, 3 females; SSI range = "mild" – "severe") Ten controls (age range = 26 – 46; 7 males, 3 females)	16 variables grouped into: Acoustic – duration Acoustic -relative timing, Physiological – duration, Physiological – relative timing.	Produced the target /p/ as the medial consonant of C_1V_1 - $C_2V_2C_3$ sequences embedded in utterances that varied in length and location of the target movement. (5 trials of 4 variants, all with voiceless C_2)	No group differences in measures of acoustic variability. Coefficient of variation for the devoicing interval and VOT was significantly larger for the stuttering group than the control group No significant differences between groups for any relative timing measures No other significant differences	Many similarities between PWS and controls. Where differences were found, they were found in the physiological variability measures only.

(Max & Yudman, 2003)	Accuracy and variability of isochronous rhythmic timing across motor systems in stuttering versus nonstuttering individuals	Strain-gauge Electrogonio meters	Head-mounted strain-gauge for speech/oro-facial movements electrogoniometers for finger tapping.	10 PWS (age range = 27 – 45 years; 7 males, 3 females; SSI range = 'mild' – 'severe') 10 age/sex matched controls.	Aperture and variability of lip movement, finger movement and non-speech lip movement.	Repetition of a movement (speech, non-speech, finger) in a synchronous way.	No significant differences between the groups for timing accuracy and timing variability. Both groups produced more variable movements as speed of timings increased.	Rethink of the classic assumption that PWS have a deficit with timing for speech, and general movements
(McClean & Tasko, 2004)	Correlation of orofacial speeds with voice acoustic measures in the fluent speech of persons who stutter	EMA	Two-dimensional motions of the upper lip, lower lip, tongue blade, and jaw.	39 PWS (mean age = 26 years; two females, 37 males; SSI range = 'mild' - 'severe'. 43 fluent controls (mean age = 23 years; one female, 42 males)	Peak speed of movement for upper lip, lower lip, tongue blade and jaw. Vowel F0 and intensity surrounding midpoint of /æ/ vowel.	Produce the utterance "a bad daba" at normal, loud, and soft vocal intensities	Controls showed stronger correlations than PWS between lip and tongue blade movement speed and F0 and sound intensity. No difference between correlations for measures of jaw and upper lip.	Smaller correlations in PWS indicate relatively reduced neural connectivity between tongue and lower lip, and respiratory-laryngeal pathways.
(McClean et al., 2004)	Orofacial movements associated with fluent speech in persons who stutter	EMA	Two-dimensional motions of the upper lip, lower lip, tongue blade, and jaw.	37 PWS (mean age = 23 years; two females, 35 males) Split into two groups based on severity: Low: <25 SSI, n = 23. High: >25, n = 14. 43 fluent controls (mean age = 26 years; one female, 42 males)	Peak speed of openings and closures for upper lip, lower lip, tongue blade and jaw for specific sounds within a nonsense phrase. 20 measurements in total. Ratios of lip and tongue speed to jaw speed.	Repetition of read, simple, nonsense phrase or long and meaningful sentence.	Group differences in speed and duration of lower lip and jaw closing movements during phrase. Group differences in speed and duration of tongue opening and closing movements during sentence. No differences in any of the other measures.	Failed to replicate findings that PWS differ in vocal tract closing movements, and ratios of lip/tongue and jaw movement speeds. Many similarities between PWS and controls. No clear pattern of results.

(Namasivayam & van Lieshout, 2008)	Investigating speech motor practice and learning in people who stutter	EMA	3 timepoints: 2 time points on day 1; 10 minutes in between time points. 3rd time point approximately 1 week later	5 male PWS (mean age = 26.1, range: 18 – 41; SSI range: "very mild" - "severe"). 5 Fluent controls (mean age = 25.3, range = 22 – 32, years)	Upper and lower lip protrusion variability, amplitude, duration and cSTI. Tongue body gestures Cyclic STI: measures cycles of lip movements as inputs to STI (Smith et al., 2000).	Repetition of bapi or bipa over 12 seconds at normal and fast rates.	PWS produced larger upper lip movements compared with controls at both normal and fast speaking rates. The upper lip amplitude of PWS was the same across rates. Trend that PWS had higher cSTI scores than controls for lower lip movement at normal speech rate only (non-significant). No Group X Practice interaction effects. Trends reported pertaining to controls responding more to practice than PWS (non-significant). Both PWS and controls showed decreased cSTI scores for LL only, at 1 week, compared to timpoint 1. No significant interactions between Group and Learning.	PWS and controls perform similarly on a number of movement control variables. PWS produced larger upper lip movements compared with controls. Could be interpreted as a mechanism to enable more feedback. No effect of practice or learning (trends reported, non-significant).
(Namasivayam et al., 2008)	Bite-block perturbation in people who stutter: immediate compensatory and delayed adaptive processes	Bite Block perturbation EMA	3 time points: Pre-bite block Immediately after bite block insertion 10 minutes after bite block insertion	5 male PWS (mean age = 26.1, range: 18 – 41; SSI range: "very mild" - "severe"). 5 Fluent controls (mean age = 25.3, range = 22 – 32, years)	Amplitude upper/lower lips Peak velocity Movement duration cSTI Relative Phase between upper and lower lips	Repetition of bapi or bipa over 12 seconds at normal and fast rates.	PWS and controls performed similarly at normal speech rates At fast speech rates PWS made larger, longer movements compared with controls. The bite-block perturbation changed co-ordination patterns of upper and lower lips for PWS but not controls.	Whilst PWS and controls performed similarly after bite block perturbation at normal speaking rates, the additional complexity of a fast speaking rate was associated with larger amplitudes and peak velocities in PWS.

(Namasivayam et al., 2009)	Sensory feedback dependence hypothesis in persons who stutter	EMA Tendon Vibration	EMA of tongue body, upper and lower lips and jaw. Masseter tendon vibration Auditory Masking	5 male PWS (mean age = 26.1, range: 18 – 41; SSI range: "very mild" - "severe"). 5 Fluent controls (mean age = 25.3, range = 22 – 32, years)	Relative phase Variability of relative phase	Repetition of /api/ (large degree of bilabial closure) or /awi/ (lower degree of bilabial closure) over 12 seconds at normal and fast rates.	Between group differences limited to when auditory masking and masseter tendon vibration were applied and the jaw was free to move. PWS showed less variability of co-ordination patterns than controls. No group differences for either of the conditions in isolation or combined.	PWS and controls were similarly effected by sensory and auditory perturbations.
(Sasisekaran, 2013)	Nonword repetition and nonword reading abilities in adults who do and do not stutter	IREDs	Movement of upper lip, lower lip and jaw.	9 PWS (Mean age = 32.2; 8 males, 1 female) 9 control participants (Mean age = 31.8; 8 males, 1 female).	Duration STI (See Smith et al., 2010)	Four 6-syllable nonwords and four 11-syllable nonwords. All nonwords started with /mæb/ and ended in a /bV/ syllable.	PWS showed greater variability and longer durations than controls. Both groups had greater variability for longer words compared with shorter nonwords. No interaction between group and length (trend, n.s). Both groups showed a decrease in variability and duration from the first 5 trials to the last 5 trials. For duration only, PWS reduced durations from first 5 to last 5 utterances more than controls. % dysfluent syllables of the PWS was positively correlated with duration. Negative correlation between change in variability from first 5 to last 5 utterances and %dysfluent.	Overall PWS showed greater variability than controls. Only descriptive effects of trial length and order were found. Stuttering severity (%dysfluent syllables) can be related to overall amount of variability and amount of practice effect of variability.
(Sasisekaran & Weisberg, 2014)	Practice and retention of nonwords in adults who stutter	IREDs	2 Time points, 1 hour between each session. Movement of upper and lower lips	10 PWS (Mean age = 30.7 years, range = 17.7–65.1 years; 9 males, 1 female; SSI range = "very mild" – "severe") 10 controls (Mean age = 30.8 years, range = 18.6–64.5 years; 9 males, 1 female).	STI of lip aperture (See smith et al., 2010)	Nonwords varying in length (3, 4, 6 syllables), phonotactic constraint (PC vs. NPC, on 3-syllable nonwords only), and complexity (simple, complex)	No main effect of group or complexity. Control participants had reduced variability scores both within and between sessions for 4 syllable words. No change for PWS.	No difference in variability between PWS and controls. Less practice and retention in PWS compared to controls

(Smith et al., 2012)	Language and motor abilities of preschool children who stutter: evidence from behavioural and kinematic indices of nonword repetition performance	IREDs	Movement of upper and lower lip.	Thirty-one preschool CWS (median age = 55, range = 48 – 71 months; 24 males, 7 females). Kinematic data on a subset of 8. 22 children who did not stutter (median age = 59, range = 48 – 72 months; 12 males, 10 females). Kinematic data on a subset of 13.	STi of lip aperture (see smith et al., 2010)	Nonwords varying in length (1 – 4 syllables) and complexity. Length control: 4 syllable, simple, nonword. first syllable/mæb/and the final consonant (/b/).	Main effect of group: CWS had higher STI scores than controls. Variability increased with word length/complexity for both PWS and controls. No word x group interaction. No significant practice effect (change in STI score from 1st 5 to last 5 utterances). Descriptive trend only. No difference in movement duration between groups across all non-words. Both CWS and controls decreased their movement duration from 1st 5 to last 5 utterances.	Children who stutter as young as 2-4 years old show greater variability, thus less motor control compared to fluent counterparts.
(Smith et al., 2010)	Increasing phonological complexity reveals heightened instability in inter-articulatory coordination in adults who stutter	IREDs	Movement of upper and lower lip.	17 PWS (age range = 18 – 45 years; 5 females, 12 males; SSI range = 'very mild' to 'mild'. 17 fluent controls matched for age, sex and education level	STi of lip aperture	Nonwords varying in length (1 – 4 syllables) and complexity. Length control: 4 syllable, simple, nonword. first syllable/mæb/and the final consonant (/b/).	Main effect of group: PWS were more had higher lip aperture STI scores than controls. Main effect of nonword: STI scores for both groups increased with complexity of the word Interaction between group and complexity: As the nonwords increased in complexity, the difference between PWS and controls increased. Main effect of practice: both groups were more variable during the first 5 repetitions compared to the second 5 repetitions. Interaction between group and practice: PWS showed greater practice effects than controls	Linguistic complexity and length of utterances contribute to decreased speech motor control in PWS moreso than controls.

(Tasko et al., 2007)	Speech motor correlates of treatment-related changes in stuttering severity and speech naturalness	EMA	Movement of upper lip, lower lip, tongue blade and jaw. Two time points: Before and after a 1 month fluency shaping and breath control treatment program	35 PWS (mean age = 24.9 years; 2 females, 33 males)	Duration Speed Movement Distance	Repetition of "a bad daba'' at habitual rate/loudness	Participants reduced severity score (SSI-3) after therapy. Participants reduced speed and amplitude of speech movements after therapy. Participants were rated as more unnatural after therapy.	Fluency shaping and breath control treatment lead to increased fluency associated with a reduction in the speed and size of articulator movement. However, participants were rated as have more unnatural speech as a consequence.
(Usler et al., 2017)	A Lag in Speech Motor Coordination During Sentence Production Is Associated With Stuttering Persistence in Young Children	IREDs	Movement data of upper and lower lips.	36 CWS split into 2 groups based on stuttering history: 21 Persistent CWS (mean age = 78.2 months; 4 girls, 17 boys) 15 Recovered CWS (mean age = 78.4 months; 5 girls, 10 boys) 31 fluent controls (mean age = 77.6 months; 11 girls).	STI of lip aperture (see Smith et al., 2010).	Sentence repetition of simple, and complex; short (6.syllables) and long (8 syllables), sentences.	Overall, higher variability was seen in longer, and more complex, sentences compared to shorter and simpler sentences respectively. Persistent CWS had higher variability compared to controls at all sentence levels. Recovered CWS were not different to controls, but a trend was seen as different to persistent group. No interactions between these measures were found. Large individual differences found in all groups, overlap between groups common. Duration and variability were not correlated for any group. Correlation between stuttering severity score and variability index for the long, complex sentence only.	High individual differences in STI score amongst PWS and controls. Group differences limited to when additional complexity was applied to the speech motor system.

(Walsh et al., 2015)	Speech motor planning and execution deficits in early childhood stuttering	IREDs	Movement data of upper and lower lips	58 CWS (age range = 4-6 years; 14 girls; SSI range = “very mild” – “severe”). 43 age-matched controls.	Velocity, Amplitude and Duration STI of Lip Aperture (See smith et al., 2010)	Repeated utterances of 'buy bobby a puppy' and 'mommy bakes pot pies' (all for STI/duration) ‘mom’ and ‘pup’ for velocity and amplitude measures	Main effect of Sex: Males had larger STI scores than females. Interaction showed this was particularly so for PWS. Male CWS had reduced amplitudes and velocity compared to male controls. No other differences for group/sex found.	Boys may have immature speech motor system which makes them more susceptible to developmental stuttering than girls who stutter. This fits in with a general developmental disorder bias towards males.
(Walsh & Smith, 2013)	Oral electromyography activation patterns for speech are similar in preschoolers who do and do not stutter	EMG	Electrodes on left and right lower lip	64 preschool CWS (age range = 3y 5m – 5y 11m; 17 girls) 40 children who do not stutter (3y 6m – 5y10m; 12 girls).	Amplitude Asymmetry Bilateral Coordination	Conversational speech Sentence repetition	No difference between CWS and controls for any of the measures. EMG amplitude was lower during disfluent compared with fluent conversational speech of CWS. No evidence of tremor in disfluent speech of CWS.	No basic differences in muscle activation patterns between CWS and controls.

See Figure 3.1 for details of the methods.

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