Using tDCS to improve speech processes in typical speakers and people who stutter

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Declaration

I, Naheem Bashir, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

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Abstract

Stuttering is a speech disorder for which treatment options are limited. Brain stimulation methods such as tDCS used as an adjunct to treatments enhance positive effects of intervention. This thesis addressed whether tDCS applied to the left inferior frontal gyrus would improve speech processes in typical speakers (TS) and people who stutter (PWS). Study 1.1 with TS showed that tDCS resulted in enhanced performance (reduction in speech reaction times) for three, but not one, syllable words in a picture naming task. Such interaction between stimuli complexity and tDCS was explored in Study 1.2. A picture-naming task was used with three syllable stimuli. Primes either facilitated the speech plan (low complexity) or required speech-plan reformulation. When anodal tDCS was applied, incongruent trials alone were significantly quicker than sham trials, replicating the effect of difficulty. Study 3 with TS applied tDCS whilst participants repeated tongue twisters. Anodal tDCS resulted in significantly faster tongue twister completion times compared to sham or cathodal stimulation. The studies with TS indicated that tDCS improves speech processes, particularly when task complexity is high. Study 4, applied tDCS to PWS alongside a challenging intervention known to reduce stuttering. There were reductions in stuttering during conversation that trended towards significance (sample size was small). Finally, we examined inferior frontal gyrus neural activity in PWS and TS whilst conversing socially or to a recording. The left inferior frontal gyrus showed significant and unique responses during face-to-face conversation compared to audio conversation. Findings indicated that the left inferior frontal gyrus is differentially involved when PWS communicate in different styles. This thesis demonstrated that tDCS is a promising adjunct for improving speech production processes in TS and PWS to use with challenging tasks and interventions. Further research is required to understand mechanisms of effect and to further refine effects for this promising approach.

Impact Statement

Current treatments for stuttering result in variable and short-term improvements in speech, lead to speech which is often perceived as unnatural, and reliance on techniques which are difficult to maintain over time and outside of clinical settings. The research in this thesis shows that brain stimulation techniques can be used to enhance speech production processes. Consequently, brain stimulation could serve as a powerful tool to augment treatments and potentially lead to long lasting stuttering changes, which transfer outside of clinical settings. Our results therefore have significant clinical impact as they can improve the effectiveness of current therapies and change how stuttering therapy is delivered. The brain stimulation technique used, transcranial direct current stimulation (tDCS) which is a technique that is cheap, portable and requires minimal training. Therefore, tDCS can be easily integrated into current therapies as an adjunct to improve their effectiveness. When the findings of our research are included in clinical work, this will therefore lead to significant improvements in the quality of life of people who stutter by providing a treatment option which results in greater stuttering reduction that persist compared to current methods. Our findings also open avenues for tDCS to enhance treatments for other neurodevelopmental speech disorders for which no other tDCS studies have been conducted to date.

The research in this thesis also presents novel findings with regards to neural activity in people who stutter during face to face conversation. This is the first study of its kind. As such, this study validates the potential of using functional near infrared spectroscopy brain imaging to examine speech production in face to face, ecologically valid contexts such as conversation. Thus, our study opens up new avenues of research exploring the basis of face to face conversation within people who stutter and typical speakers. Such studies will enhance our mechanistic understanding of stuttering, allowing for the elucidation of specific mechanisms of stuttering which can be targeted in further research.

Overall, the impact of the research within this thesis stretches across academic and clinical fields.

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List of Abbreviations

BGTC	Basal Ganglia-Thalamo-Cortical
BOLD	Blood-Oxygen-Level Dependent
CNV	Contingent Negative Variation
DS	Developmental Stuttering
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near Infrared Spectroscopy
HD-tDCS	High Definition tDCS
LIFG	Left Inferior Frontal Gyrus
mA	Milliamps
MEG	Magnetoencephalography
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
NIBS	Non-Invasive Brain Stimulation
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PWS	People Who Stutter
RIFG	Right Inferior Frontal Gyrus
SLT	Speech and Language Therapist
SRT	Speech Reaction Time
STG	Superior Temporal Gyrus
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TS	Typical Speakers
VRT	Verbal Response Time
VR	Virtual Reality

Chapter 1 – Introduction

Studies are presented in this thesis where the effects of transcranial direct current stimulation (tDCS) on speech processes in typical speakers (TS) and people who stutter (PWS) were explored. The neural activity associated with face-to-face speaking situations was also explored in TS and PWS. The ultimate goal of this thesis was to establish whether, and if so why, tDCS applied to the left inferior frontal gyrus (LIFG) affected speech production processes in TS and PWS. If tDCS is effective in enhancing speech processes, then this would establish tDCS as a method for the treatment of stuttering.

1.1 Developmental Stuttering and Treatment

Developmental stuttering (DS) is a neurodevelopmental communication disorder involving repetition, prolongations or blocks on sounds and syllables in a manner which interrupts the normal rhythm and flow of speech (Guitar, 2006; Van Riper, 1982). DS affects approximately 1% of the adult population and has a significant effect on quality of life as well as social and emotional functioning (Bloodstein, 1995; Bloodstein & Ratner, 2008; Guitar, 2014). Behavioural therapies for stuttering currently exist and can induce significant reduction of stuttering, but the effects are variable across participants (Baxter et al., 2016). Furthermore, these therapies only produce short term stuttering reduction, speech which is perceived as unnatural, and speech which is difficult to maintain over time and outside of clinical settings (Baxter et al., 2016). There is no current treatment available for stuttering which results in long-lasting stuttering reduction that is satisfactory to PWS or which is easy to maintain outside of clinical settings. Therefore, the development of novel interventions which enable fluent speech production in PWS are required (Howell, 2011).

1.2 Dysfunctional LIFG Activity in PWS

A potential target for a novel intervention to reduce stuttering is the LIFG, a region in which structural and functional impairment in PWS scales with stuttering severity (Etchell et

al., 2018). The LIFG is crucially involved in speech preparation processes (Long et al., 2016; Price, 2000) and is essential for fluent speech production, as demonstrated in lesion studies and BOLD functional magnetic resonance imaging (fMRI) studies with TS (e.g. Fiori et al., 2014; Holland et al., 2010) among other evidence. As the LIFG is dysfunctional in PWS, and this region is crucial for speech preparation, 'repair' of this region be neurostimulation should result in reduced stuttering severity.

1.3 Speech enhancement using LIFG tDCS

Modulation, and possible repair, of structurally and functionally impaired neural regions can be enacted using non-invasive brain stimulation (NIBS) methods. One NIBS method which has been shown to improve speech processes in those with impaired speech function (i.e. aphasia) is tDCS. The stimulation current delivered via tDCS interacts with ongoing task-based neural activity to produce modulatory effects that lead to enhanced cortical excitability and neural plasticity (Crinion, 2018; Reis & Fritsch, 2011; Stagg et al., 2011). The effects of tDCS also depend on task demands (Stagg et al., 2011; Woods et al., 2016). Therefore, increased task demands lead to greater tDCS effects. The standard approach to using tDCS in interventions is to combine a conventional challenging treatment that has a large effect on outcomes with tDCS, which then results in enhancement of post-treatment outcomes (Holland & Crinion, 2012). This has been sown in studies with aphasia which have demonstrated LIFG tDCS concurrent with an effective intervention over multiple sessions can lead to significantly greater positive therapeutic changes compared to when the therapy is delivered on its own (e.g. Baker et al., 2010; Marangolo et al., 2014). Consequently, the use of tDCS over the LIFG may enhance speech processes and stuttering treatments, and thus lead to reduction in stuttering in PWS.

1.4 Summary

In a series of experiments, we aimed to better understand the possibility of tDCS to improve speech processes, to explore its potential as an adjunct to therapeutic intervention for reducing stuttering in PWS. The first three studies (reported in Chapters 3 and 4) aimed to improve speech processes in young TS using LIFG tDCS to establish a proof of principle. In our fourth study (Chapter 5), we applied tDCS to the LIFG of PWS during a challenging fluency shaping therapy, which has a large effect on stuttering reduction, to see whether the neurostimulation further reduced stuttering. Finally, we conducted a functional near infrared spectroscopy (fNIRS) study (Chapter 6) to assess the role of the LIFG neural mechanism in stuttering within the context of a therapy setting (i.e. face to face conversation).

Chapter 2 – Literature Review

2.1 What is stuttering?

DS is a neurodevelopmental Axis I communication disorder that disturbs the selection, initiation, and execution of motor sequences used in fluent speech production (DSM-5 American Psychiatric Association, 2013; Carlson, 2013). DS is characterised as repetition or prolongations of sounds or syllables or words, or by frequent hesitations, pauses or silent blocks that disrupt the rhythmic flow and timing of speech production (Guitar, 2006; Van Riper, 1982).

DS is typically reported to have its onset in children under the age of 9 years (e.g. Ohasi, 1977). Around 95% of children who stutter start to stutter at around 4 years of age, with a mean onset age between 33 months (Yairi & Ambrose, 2005) and 42 months (Yairi, 1997). Some groups have estimated that one in ten children stutter by the age of four (Reilly et al., 2013) but around half of these children spontaneously recover by puberty (Howell, 2007; Howell, 2011) and recovery is sustained in 80% of these children into adulthood (Månsson, 2000). Approximately 1 in 100 children continue to stutter into adulthood, hence the prevalence of stuttering in the adult population is about 1% (Andrews, 1964; Bloodstein, 1995; Brown et al., 2005; Felsenfeld, 2002).

Stuttering affects more males than females with the male to female ratio being around 4:1 (Bloodstein, 1995; Yairi & Ambrose, 2013). The reasons given for this difference include that a larger number of girls spontaneously recover from stuttering than do boys (Yairi & Ambrose, 2005), hormonal influences (Geschwind & Galaburda, 1985), environmental aspects (Goldman, 1967; Johnson & Associates, 1959), slower early language development in boys (West & Ansberry, 1968) and genetic factors (Kidd, 1984; Suresh et al., 2006).

There is a genetic component to stuttering. This is supported by studies that show a higher incidence of stuttering in first degree relatives of PWS than in the general (Andrews et al., 1991; Felsenfeld et al., 2000; Howie, 1981). Twin studies also reveal considerably higher concordance levels of stuttering in monozygotic (20 – 90%) than in dizygotic twins (3 – 19%)

(Kidd et al., 1981; Yairi et al., 1996). However, it is worth noting that the twin studies do not find 100% concordance, indicating that stuttering is not entirely genetic. Genes are likely to interact with environmental factors (e.g. stressful and traumatic experiences, familial communication style etc.) which impact subsequently on neurodevelopment (Ambrose et al., 1997; Bloodstein & Ratner, 2008; Guitar, 2006; Ward, 2006; Yairi & Ambrose, 2013).

2.2 The effect of stuttering on quality of life

DS can adversely affect the social and emotional functioning of PWS as well as mental health. This is due to the fact that stuttering can evoke negative emotions such as fear, embarrassment, guilt, and shame (Bloodstein & Ratner, 2008). Stuttering is often compared to an iceberg in which the overt features (e.g. blocking, hesitations, pauses etc.) are situated above the surface of the water with the covert features (negative emotions) being below the water and invisible (Bloodstein & Ratner, 2008; Van Borsel, 2011). Self-report studies have shown that such negative emotions and cognitions about stuttering can have a severe detrimental effect on quality of life, interpersonal relationships and social functioning, leisure activities and career selection and progression of PWS (Hayhow, Cray & Enderby, 2002; Guitar, 2014; Iverach et al., 2009).

Blood and Blood (2016) reported that, compared to TS, PWS scored higher on self-report measures of social anxiety and were less satisfied with their lives. Such findings indicate PWS experience adverse effects on their mental well-being. In a qualitative study it was found that PWS who had undergone rigorous clinical assessment, reported detrimental effects of stuttering on their social and emotional functioning compared to TS (Tudor, Davis, Brewin & Howell, 2013). Consequently, comorbid disorders such as social anxiety are significantly more common in PWS compared to TS (Gunn et al., 2014). Blumgart et al. (2010) found, using self-report measures and structured interviews, that PWS were significantly more anxious than TS. PWS were also more likely to meet social phobia criteria,

with an estimated 40% prevalence of social phobia amongst PWS. The literature therefore indicates a strong association between persistent DS and anxiety.

2.3 What enables successful speech production?

In order to determine what happens when a person stutters, we must first consider fluent speech as a benchmark. Fluent speech production is a complex motor process that involves the selection and sequencing of phoneme and syllable units to create larger meaningful utterances i.e. words and sentences. According to Guenther and Gosh (2003), speech can be defined as a procedural skill that involves three basic steps: 1) translating intention to speak into motor plans, 2) executing motor plans in succession, whereby these units are articulated as a specific sequence of movements that coordinate the articulators with the respiratory and vocal systems (Bohland & Guenther, 2006; Duffy, 2013; Guenther, Tourville & Bohland, 2015; Hillis et al., 2004) and 3) monitoring and refining the output of these plans to maintain fluent speech. Disruptions to this process may lead to impaired speech production and stuttering.

One significant theory which proposes an account of fluent speech production, and indicates how speech may be impaired in PWS, is the EXPLAN theory (Howell, 2004). The name EXPLAN is a composite of the two processes the model describes: EX being the processes involved in executing a speech plan to produce speech, and PLAN being the processes involved in speech motor planning. The EXPLAN theory posits that speech planning and production mechanisms are interdependent, and delays in the planning of speech cause disruptions in production. Aspects of speech which may cause delays in speech motor planning include factors which require taxing speech planning, such as high speech rate and word complexity. Such factors have been shown to result in increased stuttering in PWS. If there is a delay in producing a speech plan, and the speech plan is only partially ready once execution begins, then the motor system may repeat sounds and words (for which the speech plan is ready) until the subsequent part of the speech plan arrives.

Hence, a disruption in the interface between speech planning and execution may cause stuttering like symptoms.

Whilst the EXPLAN model posited that the cerebellum was responsible for organising motor plans for output (Howell, 2004, 2007; Howell, Au-Yeung, & Sackin, 2000; Howell & Dworzynski, 2005), the model lacked direct imaging evidence. Subsequent models of speech production provide evidence-based theories of speech production provide insight as to how speech processes in PWS may break down. Based on the EXPLAN model, Lu et al. (2009, 2010) proposed a dual-route model of speech production. The model itself is based on neuroimaging findings from classic speech production tasks such as picture naming in PWS and TS. The dual-route model proposed two separate neural routes of dysfunction in PWS during speech preparation and production. It was proposed that impairments within a basal ganglia-LIFG network causes disruption in speech motor planning, and impairments in a cerebellum-premotor area network cause speech motor execution dysfunction (Howell et al., 2012; Lu et al., 2009; Lu et al., 2010). The postulations of the dual-route model are consistent with other evidence-based models of speech production.

A significant model which attempts to elucidate the neural regions involved in speech production is the evidence-based DIVA (Directions into Velocities of Articulators) model (Guenther & Ghosh, 2003). This model attempts to explain how speech production is a sensorimotor process contingent on the efficiency of several key brain regions as part of a sensorimotor neural network. As a result, the model demonstrates how impairment in key functional regions of the sensorimotor network may result in stuttering.

DIVA proposes that speech production involves both feedforward and feedback control systems within the brain. In order to produce a speech sound, appropriate cells within a 'speech sound map' located in the left premotor cortex and LIFG are first activated. The speech sound map is postulated to be where speech plans are constructed. Feedforward projections from the speech sound map transfer speech plan information to the articulatory cells, via articulator velocity and position maps within the bilateral motor cortex, in order to produce the required sound and speech. Initiation maps in the supplementary

motor area interconnect with subcortical regions such as cerebellum and basal ganglia to execute sequential movements via cues to action maps in the mouth motor cortex. A feedback loop then projects efferent copies of speech sounds from the speech sound map to auditory and sensory brain regions, such as the auditory cortex and cerebellum, which enables monitoring of the speech sound produced. When a difference between expected and actual speech output is detected in the afferent signals to the auditory cortex, auditory error maps in the posterior superior temporal gyrus are activated. These error maps then feedback to the right frontal ventral premotor cortex which then projects to the mouth motor cortex, as well as via a cerebellar-thalamic loop, enabling motor command corrections and successful fluent speech production.

Overall, theories suggest that successful (i.e. fluent) production of speech therefore depends upon very rapid dynamic interactions and information transfer from neural regions involved in auditory, somatosensory and speech motor processes (Brainard & Doupe, 2002; Hickok, Houde & Rong, 2011; Neef, Anwander & Friederici, 2015; Tourville & Guenther, 2011). If the integrity of the neural regions (and the connections between them) crucially responsible for auditory processing, motor planning and execution is compromised, stuttered speech is a likely outcome (Beal, Gracco, Lafaille & Nil, 2007; Scott, 2012; Watkins, Smith, Davis & Howell, 2008). Indeed, research demonstrates PWS present with structural and functional impairments, compared to TS, in speech critical sensorimotor regions.

2.4 Neural differences between PWS and TS

Neuroimaging research demonstrates PWS, compared to TS, display a wide variety of structural (reduced white matter integrity) and functional (over/under activations) neural abnormalities in sensorimotor regions including the LIFG; right inferior frontal gyrus (RIFG); superior and middle temporal gyrus, motor cortex, premotor cortex, supplementary motor area, angular gyrus, cerebellum and basal ganglia (Alm, 2007; Beal et al., 2007; Belyk, Kraft & Brown, 2015; Braun et al., 1997; Budde, Barron & Fox, 2014; Cai et al., 2014; Chang et al., 2009; De Nil et al., 2008; De Nil, Kroll & Houle, 2001; Fox et al., 2000; Kell et al., 2009;

Loucks, Kraft, Choo, Sharma & Ambrose, 2011; Lu et al., 2010; Neef et al., 2015; Neumann et al., 2003; Sommer et al., 2002; Toyomura et al., 2015; Watkins et al., 2008).

Neural dysfunction in PWS, compared to TS, is therefore consistently wide-ranging according to neuroimaging studies. Brown et al. (2005) identified 45 neural regions that displayed structural and/or functional abnormalities in PWS compared to TS. These abnormalities in PWS result in impaired dynamic interactions amongst cortical and subcortical sensorimotor systems that support speech motor planning, initiation, execution and monitoring (Neumann et al., 2005; Qiao et al., 2017; Watkins et al., 2008). However, there is little clarity and agreement about how the neural abnormalities observed in PWS result in stuttering (Etchell, Civier, Ballard & Sowman, 2018; Ingham, Grafton, Bothe & Ingham, 2012). For example, sites impaired in PWS such as the LIFG are also often impaired in aphasic patients (Marangolo et al., 2011) who present with speech impairment after stroke. It is unclear how damage and abnormalities within the LIFG can result in two distinct forms of fluency disorder. Despite the wide-ranging abnormalities displayed in PWS, a recent review (Etchell et al., 2018) of the past 20 years of neuroimaging with PWS highlighted LIFG dysfunction and abnormalities as being a consistent theme in the literature. This is examined further in the next section.

2.5 LIFG impairment in PWS

PWS display both structural and functional differences within the LIFG compared to TS. Structural differences refer to abnormalities in brain tissue while functional differences refer to abnormal activity and connections in intact tissue (Howell, 2011). Structural integrity of white matter is particularly crucial for efficient transfer of information across neural regions. In addition, grey matter is necessary for modulating action potential distributions. Thus, intact grey and white matter are necessary for healthy and efficient neural function and communication between regions (Fields, 2008). If the structural integrity of grey and white matter in speech production regions and networks is compromised, this is likely to result in impaired speech production (Watkins et al., 2008).

PWS exhibit significant structural differences in the LIFG compared to TS. Grey matter abnormalities which are correlated with stuttering severity (Beal et al., 2015; Chang et al., 2008; Kell et al., 2009; Lu et al., 2012) have been observed. In addition, PWS display white matter abnormalities and reduced connectivity to other sensorimotor regions such as the RIFG (Cai et al., 2014; Choo et al., 2011; Civier et al., 2015; Cykowski et al., 2010; Kell et al., 2009), temporal regions such as the superior temporal gyrus (Chang et al., 2011; Cieslak et al., 2015; Connally et al., 2014; Watkins et al., 2008) and to speech motor regions such as the orofacial motor cortex and premotor cortex (Chang et al., 2011; Loucks et al., 2011; Lu et al., 2010; Neumann et al., 2005).

PWS further exhibit significant functional differences in the LIFG compared to TS. A consistent finding across literature is that the LIFG is underactive during speaking in PWS compared to TS, a difference which is linked to increased stuttering severity (Budde et al., 2014; Etchell et al., 2018; Fox et al., 1996; Kell et al., 2009; Lu et al., 2010; Neef et al., 2015; Neumann et al., 2005; Sowman et al., 2012; Toyomura et al., 2011; Watkins et al., 2008; Wu et al., 1995).

These consistent findings of structural and functional differences in the LIFG of PWS, compared to FS, demonstrate that the LIFG is significantly impaired compared to FS. According to dual-route (Lu et al., 2009, 2010) and DIVA (Guenther & Ghosh, 2003) models of speech production described in 2.3, the LIFG is a sensorimotor hub critical for speech planning. If the LIFG is impaired, then it follows that speech planning processes are likely to be impaired. Furthermore, LIFG impairment is also likely to impair dynamic interactions and information transfer (via action potentials and neuronal firing) with interconnected sensorimotor regions. Consequently, LIFG dysfunction in PWS is perhaps a significant contributing factor to persistent stuttering due to producing impairments in speech motor planning and the efficient transfer of speech plans to the motor cortex for execution. Research has consistently demonstrated LIFG dysfunction leads to impairments in the process of speech motor planning and the transfer of these plans for motor execution and consequent fluent speech production.

2.6 Involvement of LIFG in speech motor planning

The first evidence about the involvement of the LIFG in speech production came from Pierre Paul Broca (Broca, 1861; Dronkers, 1996). He reported two cases of brain injury, where the LIFG was affected, which resulted in speech dysfunction (i.e. aphasia). Broca's work provided the foundation for our current understanding of LIFG function, which has been further elucidated through neuroimaging methods. Research demonstrates that the LIFG is crucially involved in speech motor planning processes and transfer of these plans to the motor cortex for execution (Bouchard, Mesgarani, Johnson & Chang, 2013; Flinker et al., 2015; Hills et al., 2004; Kuriki et al., 1999; Long et al., 2016).

Using direct cortical recordings during spoken repetition of written and spoken words, Flinker et al. (2015) LIFG activity was most prominent prior to articulation rather than during articulation itself. Hence, the authors interpreted this finding to demonstrate that the LIFG acts as a key hub of speech motor planning and execution through coordination information transfer with the sensorimotor network and motor cortex. Similar findings were also reported by Bouchard, Mesgarani, Johnson and Chang (2013), who also used high-resolution, multi-electrode cortical recordings to examine neural activity during the production of consonant-vowel syllables. Further evidence consistent with the LIFG being involved in speech motor planning comes from Kuriki et al. (1999) who demonstrated, using magnetoencephalography (MEG), that LIFG activity spikes 120-320ms prior to speech production.

Neuroimaging studies with lesioned individuals also highlight critical involvement of the LIFG in speech motor planning and subsequent speech production. For example, using Magnetic Resonance Imaging (MRI), Hillis et al. (2004) assessed 80 post-stroke patients and found a strong association between LIFG impairment and apraxia, which is characterised by difficulty in initiation of speech motor plans.

A focal cooling has also been used to elucidate the involvement of the LIFG in speech motor planning. Focal cooling involves reducing the temperature of specific cortical regions directly in awake neurosurgical patients and seeing whether this temporarily impedes functions. Long et al. (2016) focally cooled the LIFG and speech motor cortex

whilst patients vocalised speech sequences. It was found that cooling of the LIFG specifically resulted in reduced speech rate in participants, whereas cooling the speech motor cortex affected articulation quality. As LIFG cooling affected speech rate, rather than speech quality, indicates LIFG involvement in speech planning processes rather than production, and possible slowed transfer of speech motor plans to the speech motor cortex for articulation.

Consistent with the dual route (Lu et al., 2009, 2010) and DIVA (Guenther & Ghosh, 2003) models of speech production, evidence shows the LIFG is critically involved in speech motor planning and transfer of speech plans to sensorimotor regions involved in plan execution and speech production (see Price, 2010 for a review). Therefore, in PWS, the observed structural and functional impairment in the LIFG probably contributes to stuttering due to impaired formulation of speech plans (functional impairment) and impaired transfer of speech to the motor cortex (structural impairment) for execution of the speech commands (Lu et al., 2010; Neef et al., 2015).

Despite compelling evidence of functional and structural impairment of the LIFG in PWS, no current treatments for stuttering are based on potential implications that these neurological impairments have on stuttering. If impairment to the LIFG is central to stuttering, then improved processing in this region is likely to reduce stuttering. Normalising activity within the LIFG in PWS, compared to FS, could potentially lead to improvements in speech motor planning and improvements in transfer of speech motor plans to the speech motor cortex. Thus, enhancing functional and structural qualities of the LIFG in PWS is theoretically a viable avenue for treatments to reduce stuttering and improve speech fluency in PWS. Functional and structural enhancements to neural regions can be achieved through the use of NIBS methods.

2.7 Non-invasive brain stimulation (NIBS)

The use of electrical stimulation to modulate or study the brain trace as far back as 131-401 AD, where fish with electrical properties were used to treat headaches and epilepsy

(Priori, 2003). Work from Galvani and Aldini (1792) and Volta (1816) established that electrical currents could induce muscular contractions in lifeless bodies of animals and humans (Piccolino, 1998). Interest in the use of electricity then moved to using electricity to treat conditions and complaints such as melancholia (Priori, 2003). These experiments are arguably the origin of modern therapies using electrical stimulation to treat a variety of disorders (Elliott, 2014).

Merton and Morton (1980) first demonstrated that passing small electrical currents through the human scalp can modulate the brain and affect behaviours subserved by the underlying brain region that was stimulated. Since research points to neural areas that are malfunctioning in PWS to create stuttering, it may be possible to change activity within these regions by using NIBS to enhance the effects of stuttering reducing therapies that would then improve speech control. Since Merton and Morton's (1980) research, two methods have emerged as mainstays of NIBS in both basic and clinical contexts: transcranial magnetic stimulation (TMS) and tDCS.

TMS is a non-invasive brain stimulation technique that involves using magnetic fields to stimulate a cortical area of interest. Specifically, TMS delivers electrical current through a magnetic coil placed on an individual's head, and this current produces a magnetic field that lasts for approximately a millisecond. The magnetic stimulation creates an electrical field that can be large enough to lead to changes in neuronal activity and, with enough current, cause action potentials in the neurons being stimulated (Sandrini, Umilta & Rusconi, 2011). tDCS involves a painless, low level direct electrical current of 1- 2 mA (milliamps) delivered through surface electrodes placed over the target area on the scalp. Applying the current to the scalp results in a less focal stimulation compared to TMS, as the current flow can be distorted by a number of factors including the conductivity of the different tissue types it passes through (Sadleir et al., 2010). Although the vast majority of the electric field is absorbed by the scalp and cerebral spinal fluid, a small yet significant electric field reaches the cortex (Nitsche et al., 2008). Stimulation with tDCS does not typically discharge action potentials, but rather modulates the resting membrane potential of underlying neuronal

tissue, resulting in increased or decreased spontaneous neural firing with anodal and cathodal tDCS respectively (Nitsche et al. 2003; Nitsche & Paulus, 2000; Stagg & Nitsche, 2011; Utz et al., 2010).

Whilst both TMS and tDCS are capable of modulating neural activity, TMS arguably induces a stronger physical sensation at the stimulation site compared to tDCS. While participants typically cannot reliably differentiate between real and sham tDCS, participants are able to distinguish between real and sham TMS almost 100% of the time (Klaus et al., 2018). Although some studies use placebo coils or stimulate several areas (i.e., including at least one control region which is not expected to affect the outcome), many studies so far have only compared performance with real TMS to performance without the application of TMS. Evidently, in these cases, participants know when they are being stimulated and this could bias results. As such, tDCS allows for better (double) blinding procedures as compared to TMS. Furthermore, tDCS is not associated with serious adverse events and requires low technical expertise and is cheap to administer. In addition, compared to TMS, tDCS can be used to induce longer lasting functional and structural neural changes which outlast the stimulation period (Klaus et al., 2018). Consequently, tDCS has significant clinical relevance and thus has emerged as a popular focus in the recent literature.

2.7.1 Safety of tDCS. Considerable amounts of research have demonstrated tDCS to be a safe procedure for use in humans (Agnew et al., 1983; Bikson et al., 2016). The intensity of the currents used in human studies are typically 1-2mA, which is substantially below those found to be safe in animals (Liebetanz et al., 2009; McCreery et al., 1990). Research has also shown that tDCS is very safe as it does not compromise brain tissue in humans (Nitsche et al., 2004). One schizophrenic patient received one to two daily stimulation sessions of up to 3mA for 30-minute sessions for three years (over 1000 stimulation sessions) without any damage or adverse events being reported (Andrade, 2013). An extensive review carried out on 567 tDCS sessions in healthy controls and individuals with symptoms of migraine, tinnitus or stroke, found the most common side

effects of tDCS were tingling under the electrode, moderate fatigue and an itching sensation (Poreisz et al., 2007). A more recent review (Brunoni et al., 2011) revealed that although side effects such as tingling and itching sensations below the electrodes were slightly higher in active stimulation conditions, this was not significantly different to sensations reported during sham stimulation. Overall, research has demonstrated that tDCS is a safe procedure to administer to human participants and it has no severe side effects.

2.7.2 Mechanisms and effects of tDCS. When tDCS is delivered, the electrical current causes an alteration of the resting membrane potential and excitability of neurons. This modulation of neuronal excitability causes an increase or decrease in the likelihood of action potential and neuronal firing (Bikson et al., 2004; Nitsche et al., 2003; Nitsche et al., 2008; Stagg & Nitsche, 2011).

Neuronal excitability is promoted by anodal current tDCS. This occurs through depolarisation of the resting membrane potential, which increases the likelihood of neuronal and action potential firing (Nitsche & Paulus, 2000; Stagg et al., 2009). In contrast, cortical excitability is inhibited by cathodal current tDCS, which induces hyperpolarisation of the resting membrane potential, reducing the likelihood of neuronal and action potential firing (Nitsche & Paulus, 2000; Stagg et al., 2009). Increasing or decreasing excitability of neurons with tDCS can thus enhance or inhibit action potential firing and message transfer between synapses, strengthening or weakening synaptic connections. Synaptic connection strength affects the efficiency of information transfer between synapses, with stronger connections leading to more efficient synaptic communication. The process of strengthening or weakening of synaptic connections as a result of experience is known as synaptic plasticity.

When tDCS is applied over a targeted neural region, the region as a whole can be excited or inhibited through modulation of cortical excitability and synaptic plasticity of the populations of neurons contained within that region. Modulation of neural regions with tDCS consequently modulates the behaviour and functions associated with the region targeted with stimulation (Nitsche et al., 2003). Such effects can occur online (during stimulation) or

offline (after the end of stimulation) due to long-term depression (LTD) and long-term potentiation (LTP) plasticity mechanisms (Zaghi et al., 2009). Overall, tDCS can induce both changes in functional neural activity and structural neural changes due to online and offline effects of cortical excitability and synaptic plasticity modulation (Nitsche et al., 2004). Hence, tDCS could potentially be used to modulate neural regions with the aim of enhancing behaviour.

2.7.3 Behavioural tDCS effects. Online and offline effects of tDCS result in increased regional cerebral blood flow in the targeted area during and after stimulation (Zheng et al., 2011), as well as modulation of intracortical and interhemispheric processing (Sehm et al., 2013). Such neural effects of tDCS often result in behavioural changes as a result of tDCS modulation which interacts with task-related activity in tasks which engage the targeted neural region (Stagg et al., 2011).

Research has used tDCS to improve performance of motor, visual and cognitive tasks in healthy participants and those with acquired neural damage (for reviews see: Jacobson, Koslowsky & Lavidor, 2012; Reis et al., 2008). Facilitatory effects of tDCS on behaviour have been widely observed, ranging from motor task performance (Bolognini et al. 2011; Parikh & Cole 2014; Talelli, Greenwood & Rothwell 2007), motor skill acquisition and refinement (Hummel, 2005; Monte-Silva et al., 2010; Reis et al., 2008), perception (Antal et al., 2004), working memory (Fregni et al., 2005; Sandrini, Fertonani, Cohen & Miniussi, 2012); executive functions (Dockery, Hueckel-Weng, Birbaumer & Plewnia, 2009); declarative memory (Javadi & Walsh, 2012) and language (Monti et al., 2013).

The potential of tDCS to induce changes in cortical excitability with minimal adverse effects, when applied alongside tasks which engage the targeted region, has led to a dramatic increase in the use of tDCS as an adjunct to therapeutic interventions. Successful therapeutic applications (i.e. reduction of disorder symptoms) with tDCS applied alongside current therapies have been demonstrated with psychiatric and neurological conditions, including psychiatric disorders (schizophrenia and depression), Parkinson's disease, stroke

and in particular, the post-stroke speech impairment associated with aphasia (Allman et al., 2016; Baker, Rorden & Fridriksson, 2010; Boggio et al., 2008; Flöel, 2014; Lefaucheur et al., 2017; Marangolo et al., 2011; Mortensen et al., 2016; Price & Crinion, 2005).

2.8 tDCS in Aphasia rehabilitation

Aphasia is a term for the impairment of the understanding and/or use of spoken and/or written language following brain injury (e.g. after stroke). Critically, the mechanisms of tDCS described in 2.7.2 interact with ongoing neural activity within a task to produce modulatory enhancement or inhibition effects (Stagg et al., 2011). Speech neurorehabilitation work with tDCS in aphasia therefore applies tDCS alongside interventions to modulate cortical excitability and plasticity in aphasic patients and produce behavioural improvements of speech production.

Electrical stimulation can be used to recruit (using anodal tDCS) perilesional tissue when applied alongside aphasia interventions (Baker et al., 2010; Baker & Rorden, 2011; Campana, Caltagirone & Marangolo, 2015; Fridriksson, Richardson, Marangolo et al., 2014; Galletta & Vogel-Eyn, 2015; Shah-Basak et al., 2015). In addition, dysfunctional overactivity in the right hemisphere, which is thought to prevent functions in the left hemisphere, can be inhibited using cathodal tDCS when applied alongside aphasia interventions (Barwood et al., 2011; Cherney et al., 2013; Cipollari et al., 2015; Naeser et al., 2010; Vines, Norton & Schlaug, 2011). Hence, tDCS-assisted aphasia rehabilitation can be regarded as a way of maximising the brain's ability to re-learn and rehabilitate damaged areas which may facilitate improvement in function and achieve lasting changes (Holland & Crinion, 2012).

Aphasia rehabilitation studies have employed tDCS to see if they enhance therapies for the rehabilitation of anomia (word finding difficulty; Monti et al, 2008), as well as articulatory and speech production impairments (Marangolo et al., 2016), particularly during multi-session studies. These studies have suggested that lasting effects of stimulation may be more easily obtained with multiple stimulation sessions and coupling the stimulation with concurrent language treatments (Baker et al., 2010; Fridriksson et al., 2011; Shah-Basak et

al., 2015; Wu, Wang & Yuan, 2015). The hypothesis underlying multiple-session studies is that the short-lasting positive effects from a single session of therapy accumulates with repeated sessions and eventually leads to a permanent improvement in the treated function (Galletta, Conner, Vogel-Eyny & Marangolo, 2016).

Marangolo et al. (2011) showed that anodal tDCS over the LIFG coupled with language training over multiple sessions led to significant reduction in aphasia symptoms. Recently, the same group investigated whether similar results would be achieved using bihemispheric tDCS delivered over the LIFG and RIFG (Marangolo et al., 2016). The results showed that the number of correct syllables, words and sentences produced by patients significantly improved only after the real stimulation condition. These significant changes persisted at one week after the end of treatment. Moreover, this improvement generalised to other oral tasks (picture description, noun and verb naming, word repetition and reading).

Other studies have demonstrated the effectiveness of multi-session presentation combined with intervention programmes for the treatment of aphasia. Baker et al. (2010) contrasted the effects of five days of anodal tDCS (1ma, 20 minutes) over the LIFG with five days of sham tDCS during a computer-based aphasia therapy programme. Despite individual differences in chronic aphasic patients who participated in the study in terms of time since onset, lesion location and size, they found anodal tDCS was associated with a significant increase in word naming amongst participants. This improvement was maintained for at least one week. Similarly, Fridriksson et al. (2011) assessed reaction time after participants received tDCS, over the left posterior cortex, during a word-picture matching task over the course of two five-day intervention courses. In the first phase that lasted 5 days, anodal tDCS was applied over the LIFG. In the second five-day phase, sham tDCS was applied over the contralateral forehead. They found a significant improvement in reaction time in treated nouns following anodal tDCS compared to no stimulation and this was maintained for up to 3 weeks after treatment. Results therefore showed that anodal tDCS to the left hemisphere is effective in facilitating naming post-stroke, which indicates tDCS has the potential to improve speech production.

Aphasia studies have further demonstrated a specific effect of LIFG stimulation that results in improved speech production as well as improvements on naturalistic outcome measures. Marangolo et al. (2013) compared anodal tDCS over the LIFG and superior temporal gyrus (STG) in an intensive two-hour daily conversation-based intervention paradigm in aphasic patients over ten days. Patients who received LIFG tDCS achieved significantly more improvement in speech cohesion and use of function words compared to the STG stimulation group. This improvement was maintained for one month and patients showed generalisation of treatment effects outside of the clinical sessions. This study demonstrated the importance of intensity and complexity of test materials within an intervention paradigm and for maximisation of tDCS effects. The effects of tDCS depend on task demands, increased task demands lead to greater tDCS effects, due to interaction of the tDCS current with synaptic action potentials (Stagg et al., 2011; Woods et al., 2016). Therefore, high task demands are an essential part of neurorehabilitation to enable neural plasticity changes (Kleim & Jones, 2008). The results of Marangolo et al. (2013) further demonstrated that tDCS-enhanced intervention can enable generalisation of positive therapeutic outcomes, as patients showed generalisation of treatment effects outside of the clinical sessions. This may be beneficial for development of tDCS interventions with PWS, as current treatments for stuttering are difficult to maintain outside of clinical sessions (Baxter et al., 2016).

Whilst aphasia studies have demonstrated promising results for the use of tDCS as an effective adjunct to intervention, the research is inconsistent regarding its effectiveness in recovery of speech function. A Cochrane review of the effectiveness of tDCS in aphasic patients concluded that neither anodal nor cathodal tDCS showed significant improvements relative to sham tDCS in terms of functional communication, language function or cognitive impairment following stroke (Elsner et al., 2015). Although this review does not reflect the outcomes of a number of studies indicating significant improvements associated with tDCS, this may be because the authors of the Cochrane review considered previous studies to be of ‘low’ research quality. Furthermore, although the reports of therapeutic application are

generally positive, they are limited in number and, therefore, few extensive reviews of their effectiveness have been carried out.

Overall, although findings are mixed, tDCS neurorehabilitation research with aphasic patients suggests tDCS may be a promising supplementary treatment approach (tDCS applied alongside therapy) for recovery from speech and language deficits. Such research is relevant to PWS as it may demonstrate that tDCS, used alongside an appropriate intervention, could lead to modulations of impaired speech-critical brain regions and consequently lead to a reduction in stuttering.

2.9 Using tDCS to reduce stuttering in PWS

Whilst approaches which result in stuttering reduction exist, they are severely limited in their effectiveness and generalisation to non-clinical settings. Current treatment approaches to improve fluency in PWS only induce temporary effects or produce unnatural sounding speech which is effortful to maintain over time and outside of clinical settings (Baxter et al., 2016, Ingham et al., 2001). Craig and Calver (1991), for example, found that only half of PWS who underwent smooth-speech fluency-shaping therapy were satisfied with their level of fluency 12- to 18-months later. The remainder believed their speech sounded unnatural. According to a systematic review of 111 papers on non-pharmacological interventions for stuttering, most available interventions demonstrated a degree of clinical effectiveness only in some participants (Baxter et al., 2016). Effect sizes ranged from 0.10 to 14.96, indicating a wide range of effectiveness for stuttering interventions across individuals, types of therapies and studies. Baxter et al. (2016) further reported that there were participants who did not benefit from the interventions in all papers reviewed and around two thirds of the studies were considered to be at high risk of bias. Furthermore, Baxter et al (2016) noted that treatments for PWS often do not produce long-term improvement, and significant daily practice and effort is required to maintain treatment benefits.

Overall, there is currently no treatment for stuttering which results in a significant reduction of dysfluency that is satisfactory to PWS or which is easy to maintain outside of

clinical settings. All current interventions for stuttering are behavioural, and there are currently none which utilise knowledge of neurological dysfunction in PWS as a guide for developing therapy approaches to reduce stuttering (Neumann & Foundas, 2018). Therefore, the development of novel interventions, which utilise knowledge of PWS speech-related neurological dysfunction, are required to enhance therapeutic effects and enable fluent speech production (Howell, 2011). The use of tDCS is a promising avenue for development of such interventions.

2.9.1 Mechanisms of tDCS induced stuttering reduction in PWS. As described in 2.8.2, tDCS modulates cortical excitability, synaptic plasticity and neural information transfer, and consequently functional neural activity in neural populations and thus behaviour. If tDCS is used to target a region which is dysfunctional in PWS, it may be possible ameliorate stuttering through modulation of the dysfunctional region. For example, if a neural region is deactivated in PWS, compared to TS, cortical excitability and thus functional neural activity within the region could be enhanced with tDCS. If neural activity in a dysfunctional speech region is modulated in PWS to bring activity to TS levels, then it is possible this would reduce levels of stuttering in PWS.

In order to develop an effective brain-based stuttering intervention using tDCS, a key neural region involved in TS fluent speech production, which dysfunctions in PWS, must be targeted and modulated using tDCS. As summarised earlier in this chapter, research has shown that the LIFG is a key hub within the wider sensorimotor network responsible for speech production (Guenther & Ghosh, 2003), is critically involved in speech motor planning (Bouchard, Mesgarani, Johnson & Chang, 2013; Flinker et al., 2015; Hills et al., 2004; Kuriki et al., 1999; Long et al., 2016; Price, 2010), is structurally and functionally (deactivated) impaired in PWS compared to TS (Etchell et al., 2018), and this LIFG deactivation and impairment scales with severity of stuttering (Kell et al., 2009, 2018). Overall, the LIFG is crucial to fluent speech production and its dysfunction is a distinct signature of the stuttering brain. The LIFG is therefore a suitable target for intervention with tDCS in PWS.

As the dual-route (Lu et al., 2009, 2010) and DIVA (Guenther & Ghosh, 2003) models of speech production described in 2.3 suggest, fluent speech requires efficient functioning and synaptic information transfer within the LIFG for speech motor planning and transfer of speech motor plans to the motor cortex for execution. If tDCS is applied to the LIFG in PWS, alongside an intervention which enhances fluency and engages the LIFG, this could enhance cortical excitability, strengthen synaptic information transfer and enhance overall functional activity of this region. Consequently, this may lead to enhancements in speech motor planning and transfer of information to interconnected motor regions, due to increased synaptic efficacy. As synaptic plasticity is experience dependent, such enhancements in neural excitability and plasticity could potentially be reinforced and further enhanced over repeated sessions to produce structural neural changes via long-term potentiation (i.e. synaptic strengthening) plasticity mechanisms.

Hence, enhancing LIFG activity via tDCS in PWS may reduce stuttering through enhanced speech motor planning and enhanced sensorimotor integration and connectivity with the articulatory motor cortex and wider speech production network. In essence, the functionally and structurally impaired LIFG could be repaired via tDCS, through modulatory enhancement of the efficiency of neural excitability and plasticity mechanisms within the neural populations of the dysfunctional region (Busan, Battaglini & Sommer, 2017). In order to repair neural regions of dysfunction in PWS, and reduce levels of stuttering, tDCS is a promising option.

This thesis explored the possibility of using tDCS to reduce stuttering severity in PWS. Before attempting to apply tDCS with PWS, we conducted several tDCS studies with TS. The work reported in the next two chapters was aimed at establishing whether tDCS to the LIFG could be used to improve speech production processes in TS. If so, this would then provide a proof of principle that LIFG tDCS could enhance speech production processes in PWS which is the focus of the following chapter.

Chapter 3: Does tDCS improve picture naming performance in TS?

3.1 Introduction

The research reviewed in Chapter 2 indicated that the LIFG is a key region involved in speech production. Consequently, the anomalous activity observed in this region may be linked to speech dysfunction in PWS compared to TS. In this chapter we used tDCS to investigate the role of the LIFG during speech production in TS. Stepping back to tDCS work in clinical research, where most studies have been conducted, the most common assumption is that when pathological brain regions are targeted, any abnormal neural activity and excitability in these regions is "normalised" (Woods et al., 2016). Cortical excitation is usually higher in healthy than in impaired individuals. Hence normalization by tDCS should increase the excitation of impaired persons. If neuro-stimulation has any effects on the performance of TS, it follows that greater effects would be expected in impaired individuals who have lower cortical excitability. Therefore, before attempts were made to examine the effects of tDCS stimulation of LIFG in PWS, studies were conducted concerning whether anodal tDCS over the LIFG improves speech processing in TS to establish the approach that should be taken when stimulating PWS with tDCS. To this end, two studies are presented in this chapter that used tDCS to modulate speech preparation in TS.

Klaus et al.'s (2018) recent meta-analysis explored effect sizes in brain stimulation studies that sought to modulate (either inhibit and improve) speech and language production in TS. Thirty studies were included, and these allowed 45 effect sizes from 655 participants to be calculated. Analysis showed that NIBS is capable of modulating speech production in TS ($p < .0001$). Whilst the overall effect size was small at 0.289 (95% CI: 0.181–0.398), this estimate is comparable to those in similar meta-analyses that have investigated other cognitive functions in TS such as working memory (Brunoni & Vanderhasselt, 2014; Hill et al., 2016; Mancuso, Ilieva, Hamilton & Farah, 2016) and executive function (Dedoncker, Brunoni, Baeken & Vanderhasselt, 2016).

Various tasks have been used to measure speech production performance under NIBS. The most common one is picture naming (Woods et al., 2016). In picture naming

tasks, participants provide a name (usually a noun or verb) for a visual stimulus. The latency between stimulus and response onsets is the performance measure (speech reaction time, SRT). According to Damian, Vigliocco and Levelt (2001) picture naming involves several processes including nonverbal conceptual formulation, semantic and phonological processing to develop a speech plan, parsing the plan into syllables, and transformation of the motor codes for the syllables into movements of vocal articulators. Motor preparation for speech encompasses all processes up to execution of the motoric codes.

The semantic, phonological (e.g. encoding) and articulatory processes, and their coordination during picture naming are controlled by a left frontotemporal network that stretches from interior frontal to posterior superior temporal and inferior parietal regions (Flinker et al., 2015; Indefrey, 2011; Indefrey & Levelt, 2004; Price, 2000).

The IFG is involved in standard picture naming tasks. Thus, Holland et al. (2011) took MRI measures during tDCS neural modulation in TS in a picture naming task. Anodal tDCS led to quicker SRTs than did sham tDCS. Furthermore, SRTs during naming were correlated with decreases in the blood-oxygen-level dependent (BOLD) signal in the LIFG during anodal tDCS compared to sham tDCS. This effect was interpreted to be similar to the neural priming phenomenon, where task-dependent neural activity reduces alongside behavioural priming, where repeated exposure to the same or similar stimuli results in performance improvements. In the context of Holland et al. (2011), anodal tDCS alongside naming was proposed to have reduced the amount of excitatory input required to produce a naming response over the course of the naming experiment. Hence, these results demonstrated that increased excitability within the LIFG that led to faster SRT, was accompanied by a reduced BOLD signal in LIFG. In summary, anodal tDCS over the LIFG resulted in faster SRTs in picture naming tasks, which was possibly due to enhanced speech preparation processes, due to the involvement of the LIFG in speech preparation.

The two studies in the current chapter checked whether anodal tDCS delivered to LIFG affected the speech production of TS. Any effects of tDCS observed in TS are likely to be smaller than in PWS, due to differing cortical excitability between the two groups as

highlighted earlier. However, if tDCS improves speech production in TS, then this provides a proof of principle for approaches that use tDCS to improve speech production in PWS. The first experiment involved a classic picture naming task and the second used a priming task.

3.2 Classic Picture Naming Study (Study 1.1)

A point to note about the Holland et al (2011) study is that older individuals were used (62-74 years old). Neuroplasticity and cortical excitability may be reduced in older individuals. Consequently, their finding about tDCS may not apply to younger individuals. Young individuals exhibit near-optimal levels of neuroplasticity and cortical excitability (Zimmerman et al., 2013) and impaired individuals would be expected to be more responsive to neurostimulation. The suggestion that older and younger individuals may show different effects of neuro-stimulation is supported in studies such as Fecteau et al. (2007) and Boggio et al. (2011). Whereas Fecteau et al. (2007) showed that tDCS applied over the dorsolateral prefrontal cortex decreased risk behaviour in younger participants, Boggio et al. (2011) showed the opposite effect in elderly participants. The idea that tDCS differentially affects older and younger individuals is further supported by Arciniega, Gözenman, Jones, Stephens and Berryhill (2018) who showed 2ma anodal tDCS over frontal regions resulted in no effect on a visual working memory task in young individuals but a significant effect when applied to older individuals. Consequently, the current study used a picture naming study to examine tDCS-induced modulation of speech preparation processes in younger individuals for comparison with Holland et al.'s (2011) findings. This is necessary as the PWS in the intervention study are younger than those used by Holland et al. (2011). If tDCS effects can be elicited in TS, who have near optimal levels of cortical excitability, then it follows that the stimulation protocol would be likely to have a greater effect in impaired individuals with reduced cortical excitability compared to TS (Woods et al., 2011).

Picture naming studies typically employ targets that elicit a monosyllabic word response. However, since tDCS is probably affected by stimulus complexity (Bikson & Rahman, 2013), a three-syllable condition was included as well as a monosyllable condition

in the picture naming task in Study 1.1. The effects of tDCS effects are modulated by task complexity and demands (Stagg et al., 2011). Multisyllabic words place greater demand on speech preparation, as indicated by increased engagement of the LIFG when preparing multi-syllable words compared to monosyllabic words (Sörös et al., 2006). It follows therefore that 3 syllable words, which are more complex and demand more from the LIFG, would display greater effects of tDCS modulation. In addition, disruption of the LIFG via focal cooling results in slowed vocalisations and speech timing (Long et al., 2016). Taking the above into account, an increase in task-relevant LIFG activity via tDCS is, then, likely to lead to increased speech preparation efficiency which would be evident as reduction in SRTs in our picture naming task. It was hypothesised that anodal tDCS over the LIFG would result in significantly reduced SRTs for both one and three syllable words compared to sham tDCS but that the effects would be greater for the three syllable words.

3.3 Primed Picture Naming Study (Study 1.2)

As reported below, Study 1.1 showed a small but significant effect of neuro-modulation on SRTs when three syllable words were named (there was no effect for one syllable words). Consequently, speech preparation was examined further in a picture naming task that allowed task demand level to be increased. The study examined whether tDCS had an effect on re-formulation of a speech-motor production plan when the originally prepared plan was no longer valid in fluent young speakers. This was done by using primes that were veridical (congruent condition) or non-veridical (incongruent condition).

Speech preparation can be independently assessed using a prime and (after a delay) a target which requires a naming response (Tanji & Evarts, 1976). Looking at preparation first, on congruent trials the prime provides information that predicts the upcoming target and allows motor preparation for the target to be made. Conversely, the prime does not predict the target on incongruent trials, hence correct motor responses cannot be prepared. Therefore, this paradigm allows motor preparation processes to be examined. A similar paradigm was employed by Mock et al. (2015) to examine speech processes in PWS.

Mock et al. (2015) presented congruent or incongruent primes prior to target onset in their picture naming task. Congruent primes matched the upcoming target whereas incongruent primes did not match the upcoming target. If participants prepared a vocal response based on the prime, then SRTs for targets would be prolonged when the target did not match the prime (incongruent trials). This is because participants' motor preparation would need reformulation to produce the correct response to the target on incongruent trials. This requirement would consequently result in a slower SRT compared to congruent trials. Mock et al. (2015) measured electroencephalography (EEG) activity as well as SRTs. The findings confirmed that SRTs were longer for PWS than for TS only on congruent trials. The lack of an effect across participant groups on incongruent trials indicated that PWS's SRTs were not slower overall in this paradigm. EEG activity preceded the vocal response, indicating that slower SRTs were linked with planning/preparation of speech. Overall, the results demonstrated that updating speech motor plans takes longer in PWS compared to TS.

Whilst the effect of tDCS on motor preparation has been explored previously (Conley et al., 2015), no study to date has explored the use of tDCS to modulate speech preparation processes such as speech plan updating (for instance, Mock et al. (2015) did not use tDCS). This process of speech plan updating (required when there is a response to an incongruent prime) is more complex than when a prime can be used to prepare a speech plan. Our results in Study 1.1 suggested tDCS effects are sensitive to stimulus complexity. Therefore, we hypothesised that LIFG anodal tDCS would result in quicker SRTs compared to sham tDCS, and this difference would be greater for incongruent trials due to their higher complexity compared to congruent trials.

Further, to ensure specificity of findings, we employed a control region of stimulation which was also targeted. The control region selected was the RIFG, the right hemisphere homologue of the LIFG. Although there is over activation in PWS compared to TS in the RIFG, this has been reasoned to reflect compensation for the structurally deficient LIFG rather than speech preparation processes (Chang et al., 2008; Kell et al., 2009; Lu et al.,

2009; Sommer et al., 2002; Sowman et al., 2014; Watkins et al., 2008). Crucially, TS show no difference in RIFG activity during spoken compared to imagined stuttering (De Nil et al., 2008). More generally, the RIFG is thought to be involved in response inhibition, particularly of pre-potent responses rather than speech motor preparation per se (Hampshire, Chamberlain, Monti, Duncan & Owen, 2010). Stimulation of the RIFG as a control site therefore allows assessment of the specificity of any potential effects of LIFG tDCS.

3.4 General Method for Studies 1.1 and 1.2

3.4.1 Participant recruitment. Participants were recruited through the UCL SONA system. Inclusion criteria were: English as first language; right handed; no history of chronic or acute neurologic, psychiatric, or medical conditions; no speech, language or uncorrected sensory impairment; no family history of epilepsy; not on acute or chronic medication during the six months prior to testing. All participants reported normal hearing and had normal or corrected vision. Ethical approval was granted by UCL Department of Experimental Psychology Ethics Committee. Information sheets were given to participants and written informed consent was obtained.

3.4.2 Stimulation. A battery powered constant current tDCS stimulator (Magstim Company Ltd), the HDCStim device, was used. Two 5cm x 7cm electrodes were covered with saline-soaked sponges and secured with straps. In stimulation conditions, a 2mA constant current was applied for 20 minutes. A 2mA current was used as research by Ammann, Lindquist and Celnik (2017) suggested that anodal tDCS at 2 mA, but not 1 mA, significantly increased cortical excitability at the group level. This leads to fair to high reliability tDCS effects over multiple sessions when a Sham Variability-Based Threshold is used to classify responses and to track individual changes across sessions. Hence, 2 mA is the most likely intensity to induce increases in cortical excitability. Previous studies have reported that it is safe to use 35 cm^2 wet sponge over the human cortex with a direct current of 2 mA applied for up to 20 min (Iyer et al., 2005; Nitsche & Paulus, 2001). Furthermore, this

stimulation is effective in single stimulation sessions (Fagerlund, 2015; Holland et al., 2011; Volpato et al., 2013). In the sham condition, participants received real stimulation for 36s and this was then ramped down. This leads to a transient sensation that is almost indistinguishable from the effects experienced during real stimulation (Gandiga et al., 2006). Electrodes were positioned according to the international 10-20 EEG system. This is effective for accurate positioning of stimulating electrodes (Herwig, Satrapi & Schönfeldt-Lecuona, 2003). In both studies, the anodal stimulating electrode was placed at F5, which corresponds to LIFG (Naeser et al., 2010; Nishitani et al., 2005). For Study 1.2, the stimulation electrode was also placed over F6 in the anodal control group, which corresponds to the RIFG, for the control site condition. The reference electrode was placed over the contralateral frontopolar cortex (Nitsche & Paulus, 2011; Okamoto et al., 2004; Sparing et al., 2008). This arrangement is widely used in speech production studies (Ehlis, 2016; Holland et al., 2011; Volpato et al., 2013). Stimulation was applied during the task (online) as neuroimaging studies report greater cortical excitation during rather than after tDCS administration (Martin et al., 2014; Rae et al., 2013; Stagg et al., 2013).

3.5 Method – Study 1.1

3.5.1 Participants. Twenty-seven participants (13 male) were recruited. They ranged in age from 18-32 (mean = 23.15, SD = 4.25).

3.5.2 Design. The study was a double blind, 2x2 repeated measures design. The dependent variable was SRT (time from stimulus onset to response onset) in the picture naming task. The first independent variable was stimulation condition (sham or anodal tDCS) and the second independent variable was the number of syllables in the name of the stimuli (1 or 3 syllables). Stimuli were delivered in a randomised order in every session, and counterbalancing of tDCS sessions was performed.

3.5.3 Materials and task. One hundred and eight images with one and three syllable names were obtained from the BOSS and BOSS II image libraries (Brodeur et al., 2010, 2014). The pictures had a mean familiarity rating of 4.38 (range: 3.31 – 4.93), a mean complexity rating of 2.46 (range: 1.62 – 3.65), a mean object agreement rating of 4.17 (range: 2.69 – 4.94) and a mean percent agreement between name and picture of 92% (range: 79% - 100%). A further 14 images were obtained to be used as practice stimuli, which had a mean familiarity rating of 4.38 (range: 3.90 – 4.93), a mean complexity rating of 2.39 (range: 1.71 – 3.14), a mean object agreement rating of 3.94 (range: 2.91 – 4.61) and a mean percent agreement between name and picture of 92% (range: 90% - 93%). A classic picture naming task was used. Each picture was presented for 3000ms with a fixation cross presented for 3000ms between stimuli. The participant was required to name the stimulus as quickly and as accurately as possible after presentation. Participants named each 3-syllable item once, and each one-syllable stimulus three times to give the same articulatory load for the two syllable types and to adjust for the different planning times of words of different length (Levelt, Roelofs & Meyer, 1999). Ten second breaks were given after every 10 images. The entire study lasted around 20 minutes. All stimuli were presented in a randomised order using PsychoPy (Peirce, 2007). Responses were recorded using Audacity via a Yeti USB microphone positioned at approximately 20 degrees from vertical and 20 cm from a participant's mouth.

3.5.4 Procedure. Participants were randomly allocated to anode or sham stimulation which was decided before agreement to participate was given. Both the experimenter and participant were blind to this manipulation. This prevented potential allocation bias. After the microphone, computer and tDCS equipment had been set up, participants were asked if they were ready. Standard text instructions were presented onscreen. The instructions informed participants to respond as quickly and accurately as possible. Following this there was a practice run involving 14 stimuli. Any mistakes made during this run, such as not repeating the 1-syllable stimuli three times, were corrected by

the experimenter. Onscreen text asked if the practice run was 'OK'. Participants then initiated the experimental session from the keyboard. Order of syllable conditions was alternated between participants to control for any order effects. Participants completed the test twice, once under each stimulation condition, with a washout period of 60 minutes in-between to minimise carry-over effects (Nitsche et al., 2007). Participants were permitted to leave the test environment during this period. The same stimuli were used in the second session, but stimuli were presented in a different random order.

3.5.5 Data analysis. Inferential tests used SPSS 22.0. SRTs were made manually on oscillographic displays in Speech Filing System (STS; https://www.phon.ucl.ac.uk/resource/sfs/) to ensure that the SRTs were accurate. The onset of each stimulus and the beginning of the response was annotated manually onto the audio waveforms. SRTs were calculated as the duration, in seconds, between stimulus offset and participant response onset. Trials where an image was incorrectly named or contained irrelevant vocalisation (e.g. "umm" or "err") preceding the response were noted and removed (<1%).

3.6 Results – Study 1.1

3.6.1 Subject Analysis. A repeated measures ANOVA was conducted to assess the effect of anodal and sham tDCS on one and three syllable picture naming SRTs on a participant level. The two factors in the ANOVA were stimulation condition (anodal or sham) and number of syllables (one and three). A significant interaction was followed up using paired-sample t-tests.

The ANOVA showed a significant main effect of stimulation (F (1,26) = 8.525, p = .007), indicating SRTs were quicker in the anodal tDCS condition (mean: .846, SE: .018) compared to the sham tDCS condition (mean: .883, SE: .021). A significant main effect of number of syllables (F (1,26) = 8.313, p = .008) was also observed, indicating SRTs for three syllable words (mean: .893, SE: .018) were longer than SRTs for one syllable words

(mean: .835, SE: .021).There was also a significant interaction between stimulation condition and number of syllables (F (1,26) = 4.709 p = .039), indicating SRTs were different across anodal and sham tDCS conditions, for one and three syllable word conditions.

This interaction was examined further with two follow-up paired-sample t-tests, to examine differences between anodal and sham stimulation in one and three syllable conditions. As shown in Figure 1, the t-tests revealed no significant difference in SRT for one-syllable words (t (26) = -1.096, p = .283) between the sham (mean: .842, SD: .112) and anodal (mean: .827, SD: .112) tDCS conditions. For three-syllable words, a significant decrease in SRTs was observed (t (26) = -3.203, p = .004), indicating anodal tDCS (mean: .864, SD: .084) led to quicker SRTs compared to the sham stimulation condition (mean: .922, SD: .123).

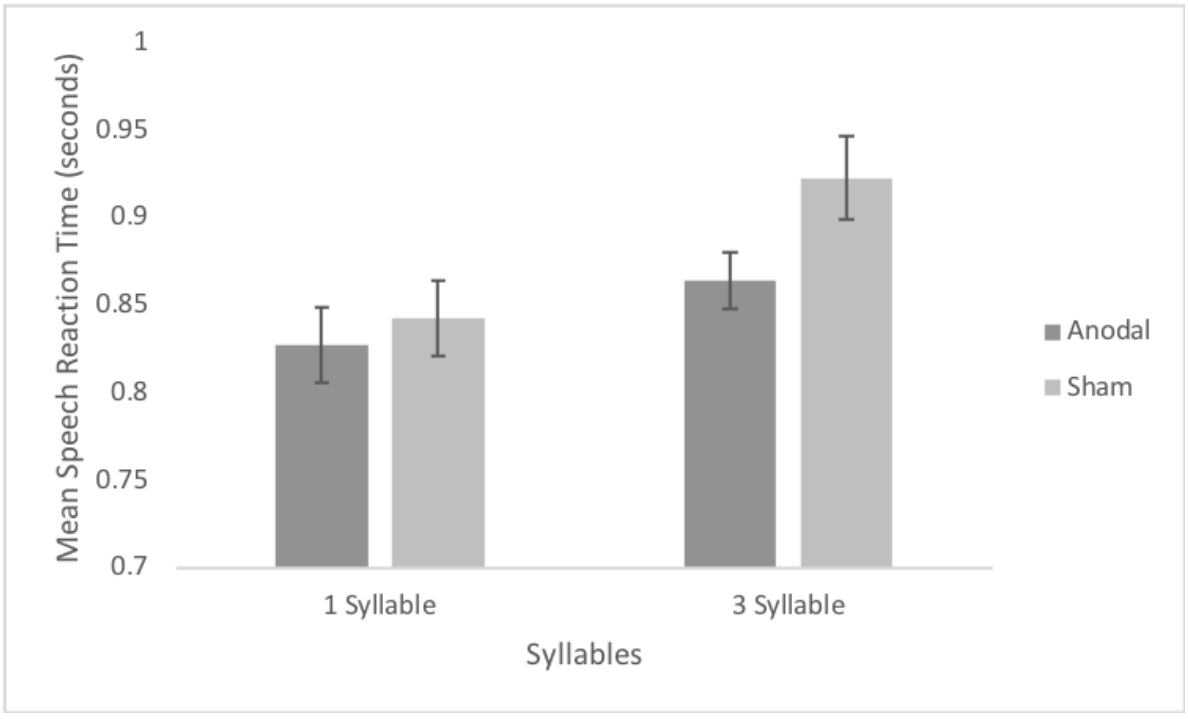

Figure 1. Comparison of subject mean SRTs (seconds) across 1 and 3 syllable conditions for anodal and sham tDCS conditions. Error bars indicate +/- one standard error.

3.6.2 Item Analysis. A repeated measures ANOVA was conducted to assess the effect of anodal and sham tDCS on one and three syllable picture naming SRTs on an item

level. The two factors were stimulation condition (anodal or sham) and number of syllables (one and three) in the ANOVA. A significant interaction was followed up using paired-sample t-tests.

The ANOVA showed a significant main effect of stimulation ($F(1,53) = 9.544$, $p = .003$), indicating SRTs were quicker in the anodal tDCS condition (mean: .819, SE: .005) compared to the sham tDCS condition (mean: .841, SE: .007). A significant main effect of number of syllables ($F(1,53) = 10.711$, $p = .002$) was also observed, indicating SRTs for three syllable words (mean: .845, SE: .006) were longer than SRTs for one syllable words (mean: .814, SE: .007). There was also a marginally significant interaction between stimulation condition and number of syllables ($F(1,53) = 3.888$ $p = .054$), indicating SRTs were different across anodal and sham tDCS conditions, for one and three syllable word conditions. This interaction was examined further with two follow-up paired-sample t-tests, to examine differences between anodal and sham stimulation in one and three syllable conditions.

As shown in Figure 2, the t-tests revealed no significant difference in SRT for one-syllable words ($t(53) = .540$, $p = .591$) between the sham (mean: .818, SD: .077) and anodal (mean: .810, SD: .051) tDCS conditions. For three-syllable words, a significant decrease in SRTs was observed ($t(53) = 3.809$, $p < .001$), indicating anodal tDCS (mean: .826, SD: .052) led to quicker SRTs compared to the sham stimulation condition (mean: .863, SD: .065).

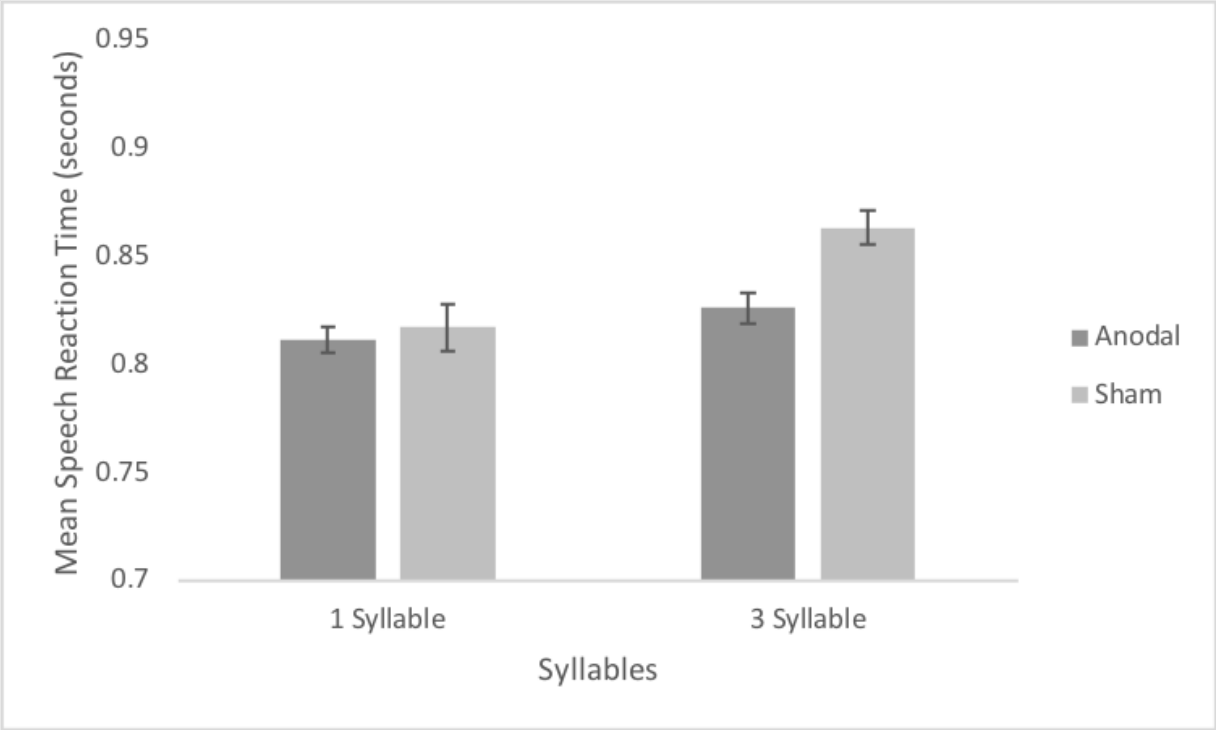

Figure 2. Comparison of item mean SRTs (seconds) across 1 and 3 syllable conditions for anodal and sham tDCS conditions. Error bars indicate +/- one standard error.

3.7 Method – Study 1.2

3.7.1 Participants. Two sets of participants were recruited via the UCL SONA research participation system and opportunity sampling for the LIFG and RIFG stimulation conditions. In the LIFG condition, there were thirty participants (15 male) who ranged in age from 18-34 years (mean = 23.63; SD=4.07). In the RIFG condition, there were twenty-eight participants (12 male) who ranged in age from 18-30 years (mean = 25.85; SD = 4.68). Participants attended for two sessions, which were separated by a 2-hour washout period. The exclusion criteria ensured factors that could have affected speech processing and SRTs did not differ across groups.

3.7.2 Design. The study used a double blind, 2x2 repeated measures design. The dependent variable was SRT (stimulus onset to response onset) and the independent variables were the stimulation condition (sham, anodal) and the hemisphere to which

stimulation was applied (LIFG or RIFG). Stimuli were delivered in a random order for every session.

3.7.3 Materials and task. Sixty pictures with similar familiarity (mean familiarity = 4.42/5 where high numbers indicate high familiarity; range: 3.62 – 4.83), image complexity (mean complexity = 2.46/5 middling complexity, range: 1.62 – 3.65) and object agreement (mean agreement = 4.28/5 where high numbers indicate high agreement, range: 2.91 – 4.94) ratings were selected from the BOSS (Brodeur et al., 2010) and BOSS II (Brodeur et al., 2014) libraries. BOSS statistics showed a mean 98% agreement between name and picture (range: 95% - 100%). Each trial comprised a word (displayed for 1500ms), a blank screen (500 ms), a picture (500 ms) and a response interval. In congruent trials, the prime word and the picture corresponded (e.g. “APPLE” was followed by a picture of an apple). On incongruent trials, the prime word and picture did not match (e.g. “APPLE” was followed by a picture of a banana). Participants were asked to name the object in the picture as quickly and as accurately as possible. All 60 stimuli were employed in each test session but presented in different random orders across sessions. In each session, the 60 stimuli were repeated in across three blocks with short breaks between blocks. There were 12 incongruent and 48 congruent trials per block (ratio of 1:4). An additional 20 images were used as practice images, which had a mean familiarity rating of 4.36 (range: 3.31 – 4.93), a mean complexity rating of 2.42 (range: 1.71 – 3.17), a mean object agreement rating of 4.01 (range: 2.91 – 4.64) and a mean percent agreement between name and picture of 92% (range: 90% - 94%).

PsychoPy software (Peirce, 2007) was used for stimulus presentation. Speech was recorded on a Macintosh laptop running Audacity software. A Yeti USB microphone was positioned 20 cm from each participant’s mouth and approximately 20 degrees from vertical for recording responses.

3.7.4 Procedure. Participants were shown the pictures used in the task as practice, and items given incorrect names were corrected by the experimenter. This ensured the accuracy of responses to pictures. As the items were high in familiarity, very few image names required correction across participants (n = 5). The experimenter then ran through every image a second time; ensuring participants named all items correctly before proceeding to practice. There were 20 practice trials in total. After practice, the experimenter ran through the names of the experimental images with the participant. This was also done twice, as with the practice stimuli, to ensure accuracy of responses. The experimental session then began. Participants completed two sessions, once without (baseline session) and once with (tDCS session) anodal or sham tDCS Stimulation. The two sets of participants in this study received tDCS either over the LIFG or the RIFG. The two sessions each lasted approximately 20 minutes and were performed on the same day with a two-hour washout period between sessions to minimise carry-over effects (Nitsche & Paulus, 2001). This was increased from the one-hour washout period in Study 1.1 in order to reduce the possibility of activation of homeostatic mechanisms which act to reduce excessive levels of neural activation (Fertonani & Miniussi, 2016). Order of sham and stimulation tDCS was randomised across participants to avoid order effects.

3.7.5 Data analysis. Inferential tests used SPSS 22.0. SRTs were obtained as in Study 1.1. Audio files were imported into SFS, and time of stimulus onset and response onset were manually marked onto the audio waveforms. SRTs were calculated as the duration between picture onset and onset of utterance. Trials with SRTs of less than 100ms or where there were errors were excluded (<1%). Analysis was conducted to assess whether a prime that corresponded to the subsequent picture (congruent) facilitated SRTs. This was assessed by comparing to when a prime did not correspond (incongruent). This was evaluated for sham and anodal stimulation groups for baseline sessions (where tDCS equipment was not in place) and tDCS sessions (where the tDCS equipment was in place) for both the LIFG and RIFG. Mixed ANOVA's were conducted with factors of tDCS session

(baseline or stimulation), tDCS type (anodal or sham) and stimulation site (LIFG or RIFG) for both congruent and incongruent stimuli. Furthermore, the LIFG and RIFG SRTs were analysed further in ANOVAs. Two mixed ANOVA's were conducted (one for congruent and one for incongruent stimuli) on SRTs for each ROI. The within subject's factors were tDCS session (baseline and stimulation tDCS) and site (LIFG and RIFG) and tDCS type was the between subject's factor (sham or anodal tDCS). The effect of tDCS on SRTs was assessed. Follow up independent samples t-tests were conducted when effects were significant. Analysis was conducted for both subject data and item data.

3.8 Results – Study 1.2 Subject Analysis

An ANOVA assessing the impact of stimulation site and tDCS type on congruent trial SRT's showed no significant effects (Table 1). A second ANOVA (Table 2) assessing the impact of stimulation site and tDCS type on incongruent trial SRT's showed no significant main effects. However, significant interactions between tDCS type and session ($F(1, 26) = 4.875$, $p = .036$), tDCS type and site of stimulation ($F(1, 26) = 6.175$, $p = .020$), and between tDCS type, site of stimulation and session ($F(1, 26) = 4.646$, $p = .041$) were observed. These interactions suggested tDCS stimulation (anodal or sham) differentially affected SRTs when participants received tDCS (as opposed to no tDCS) when applied to the LIFG or RIFG. Further ANOVA's were conducted to explore these significant interactions.

Table 1.

Results of the congruent stimuli ANOVA across tDCS type (anodal or sham), stimulation session (baseline or stimulation) and site (LIFG or RIFG) for subject data

	***F*-value**	***p*-value**
tDCS Type	2.147	.155
tDCS Type * Stim Session	1.616	.215

Site	.002	.968
Site * Stim Session	.013	.911
tDCS Type * Site	1.081	.308
tDCS Type * Site * Stim Session	.011	.917

Table 2.

Results of the incongruent stimuli ANOVA across tDCS type (anodal or sham), stimulation session (baseline or stimulation) and site (LIFG or RIFG) for subject data. Rows in bold show significant effects

	***F*-value**	***p*-value**
tDCS Type	1.277	.269
tDCS Type * Stim Session	**.4875**	**.036**
Site	.726	.402
Site * Stim Session	.115	.737
tDCS Type * Site	**6.175**	**.020**
tDCS Type * Site * Stim Session	**4.646**	**.041**

3.8.1 Analysis of LIFG congruent stimuli alone (black bars in Figure 3). The main effect of tDCS session (F (1, 28) = 5.677, p = .024) on SRTs was significant, indicating SRTs were faster when tDCS (anodal or sham) was applied (mean: .395, SE: .028) as opposed to not applied (mean: .442, SE: .036). The interaction between tDCS session and tDCS type was however not significant (F (1,28) = 1.340, p = .257). An independent samples t-test was conducted on the mean SRT difference (Table 3) between anodal and sham conditions. There was no significant difference between sham and anodal tDCS conditions at baseline (t (28) = -.359, p = .723). Anodal tDCS resulted in slightly reduced SRTs for the

with tDCS session but this was not significant (t (28) =.342, p = .735). Thus, SRTs were not affected differently when participants were presented with anodal or sham tDCS for these stimuli.

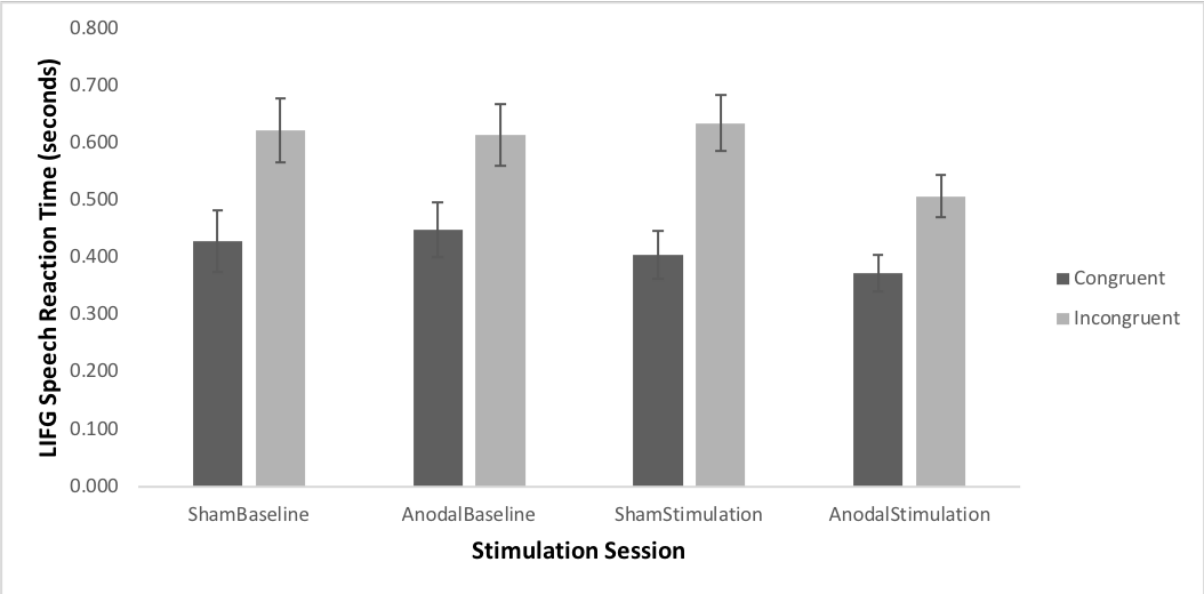

Figure 3. LIFG subject mean SRTs (seconds) for congruent (black bar) and incongruent (grey bar) stimuli for sham and anodal stimulation separately for baseline and stimulation sessions. Error bars indicate +/- one standard error.

Table 3.

Mean (SD) SRTs (seconds) for congruent stimuli across baseline and stimulation sessions for the LIFG group for subject data

	Baseline	Stimulation
Anodal	.456 (.188)	.385 (.143)
Sham	.428 (.210)	.404 (.165)

3.8.2 Analysis of LIFG incongruent stimuli alone (grey bars in Figure 3). The main effect of tDCS session (*F* (1, 28) = 4.486, p = .043) on SRTs was significant, indicating SRTs were faster when tDCS was applied (mean: .568, SE: .030) as opposed to not applied

(mean: .612, SE: .039). In addition, the interaction between tDCS session and tDCS type was significant (*F* (1,28) = 7.365, p = .011), indicating tDCS (anodal or sham) differentially affected SRTs when applied compared to not applied. This significant interaction was followed up with independent samples t-tests conducted on the mean SRT difference (Table 4) between anodal and sham conditions. There was no significant difference between sham and anodal tDCS conditions at baseline, when tDCS was not applied (t (28) = 0.275, p = .786). Anodal tDCS (mean: .501, SD: .139) however resulted in significantly reduced SRTs compared to sham tDCS (mean: .634, SD: .186) for the with tDCS session (t (28) = -1.223, p = .034). These results suggest anodal tDCS, compared to sham tDCS, resulted in significantly faster SRTs for incongruent stimuli.

Table 4.

Mean (SD) SRTs (seconds) for incongruent stimuli across baseline and stimulation sessions for the LIFG group for subject data

	Baseline	Stimulation
Anodal	.601 (.209)	.501 (.140)
Sham	.622 (.217)	.634 (.186)

3.8.3 Analysis of RIFG congruent stimuli alone (black bars in Figure 4). The main effect of tDCS session (*F* (1, 26) = .059, p = .810) on SRTs was not significant. The interaction between tDCS session and tDCS type was also not significant (*F* (1,28) = .588, p = .450). Inspection of means revealed SRT's were similar between sham and anodal (anodal mean = .420; SD = .162; sham mean = .397; SD = .163) tDCS conditions at baseline and when tDCS was applied (anodal mean = .401, SD = .149; sham mean = .408; SD = .170).

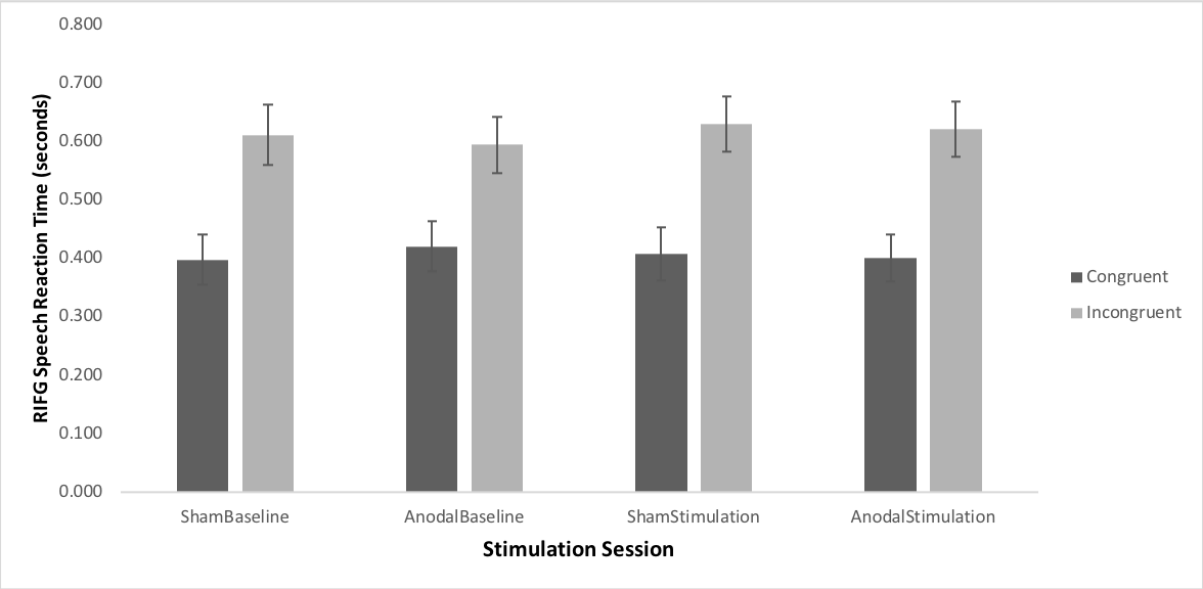

Figure 4. RIFG subject mean SRTs (seconds) for congruent (black bar) and incongruent (grey bar) stimuli for sham and anodal stimulation separately for baseline and stimulation sessions. Error bars indicate +/- one standard error.

3.8.4 Analysis of RIFG incongruent stimuli alone (grey bars in Figure 4). The main effect of tDCS session (F (1, 26) = 1.678, p = .207) on SRTs was not significant. The interaction between tDCS session and tDCS type was also not significant (F (1,26) = .049, p = .826). Inspection of means revealed SRT's were similar between sham and anodal (anodal mean = .611; SD = .190; sham mean = .590; SD = .179) tDCS conditions at baseline and when tDCS was applied (anodal mean = .620, SD = .177; sham mean = .630; SD = .174).

3.8.5 Summary. Results showed anodal tDCS over the LIFG, compared to sham, resulted in significantly faster speech updating on incongruent trials. No significant effects for congruent stimuli were observed. Finally, no effects were observed for RIFG stimulation other than differences between congruent and incongruent stimuli.

3.9 Results – Study 1.2 Item Analysis

An ANOVA assessing the impact of stimulation site and tDCS type on congruent trial SRT's showed no significant effects (Table 5). A second ANOVA (Table 6) assessing the impact of stimulation site and tDCS type on incongruent trial SRT's showed a significant main effect of site ($F(1, 70) = 19.345$, $p = <.001$), indicating LIFG tDCS (mean: .584, SE: .004) resulted in significantly faster SRTs compared to RIFG tDCS (mean: .604, SE: .004). Significant interactions between tDCS type and session ($F(1, 70) = 42.347$, $p = <.001$), tDCS type and site of stimulation ($F(1, 70) = 17.542$, $p = <.001$), session and site of stimulation ($F(1, 70) = 59.887$, $p = <.001$), and between tDCS type, site of stimulation and session ($F(1, 70) = 36.561$, $p = <.001$) were observed. These interactions suggested tDCS stimulation (anodal or sham) differentially affected SRTs when participants received tDCS (as opposed to no tDCS) when applied to the LIFG. Further ANOVA's were conducted to explore these significant interactions.

Table 5.

Results of the congruent stimuli ANOVA across tDCS type (anodal or sham), stimulation session (baseline or stimulation) and site (LIFG or RIFG) for item data

	***F*-value**	***p*-value**
tDCS Type	1.669	.197
tDCS Type * Stim Session	1.124	.290
Site	1.839	.176
Site * Stim Session	.847	.358
tDCS Type * Site	2.684	.102
tDCS Type * Site * Stim Session	2.689	.102

Table 6.

Results of the incongruent stimuli ANOVA across tDCS type (anodal or sham), stimulation session (baseline or stimulation) and site (LIFG or RIFG) for item data. Rows in bold show significant effects.

	***F*-value**	***p*-value**
tDCS Type	3.072	.084
tDCS Type * Stim Session	**42.347**	**<.001**
Site	**19.345**	**<.001**
Site * Stim Session	**17.542**	**<.001**
tDCS Type * Site	**6.175**	**<.001**
tDCS Type * Site * Stim Session	**4.646**	**<.001**

3.9.1 Analysis of LIFG congruent stimuli alone (black bars in Figure 5). The main effect of tDCS session on SRTs was not significant (*F* (1, 286) = 2.589, p = .109). In addition, the interaction between tDCS session and tDCS type was also not significant (*F* (1,286) = .057, p = .811). An independent samples t-test was conducted on the mean SRT difference (Table 7) between anodal and sham conditions. There was no significant difference between sham and anodal tDCS conditions at baseline (t (286) = -.991, p = .323). Thus, SRTs were not affected differently when participants received anodal or sham tDCS for these stimuli.

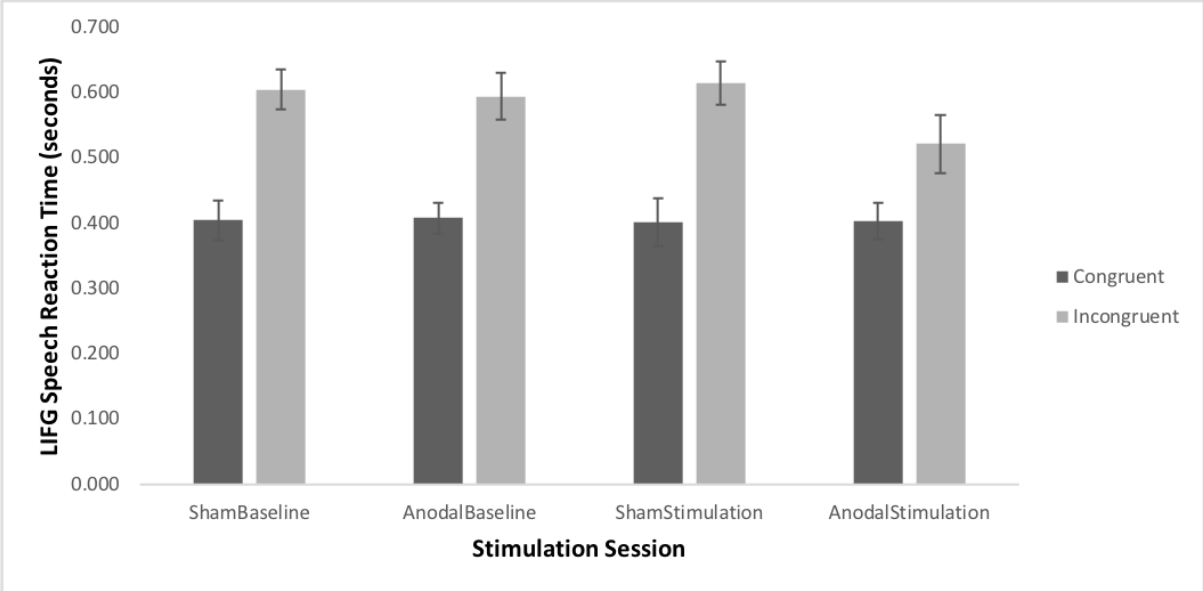

Figure 5. LIFG item mean SRTs (seconds) for congruent (black bar) and incongruent (grey bar) stimuli for sham and anodal stimulation separately for baseline and stimulation sessions. Error bars indicate +/- one standard error.

Table 7.

Mean (SD) SRTs (seconds) for congruent stimuli across baseline and stimulation sessions for the LIFG group for item data

	Baseline	Stimulation
Anodal	.409 (.023)	.403 (.027)
Sham	.405 (.031)	.401 (.036)

3.9.2 Analysis of LIFG incongruent stimuli alone (grey bars in Figure 5). The main effect of tDCS session (F (1, 70) = 89.043, p = <.001) on SRTs was significant, indicating SRTs were faster when tDCS was applied (mean: .578, SE: .005) as opposed to not applied (mean: .600, SE: .004). In addition, the interaction between tDCS session and tDCS type was significant (F (1,70) = 147.858, p = <.001), indicating tDCS (anodal or sham) differentially affected SRTs when applied compared to not applied. This significant interaction was followed up with independent samples t-tests conducted on the mean SRT

difference (Table 8) between anodal and sham conditions. There was no significant difference between sham and anodal tDCS conditions at baseline, when tDCS was not applied (t (70) = 1.349, p = .182). Anodal tDCS (mean: .551, SD: .044) however resulted in significantly reduced SRTs compared to sham tDCS (mean: .613, SD: .033) for the with tDCS session (t (70) = 9.972 p = <.001). These results suggest anodal tDCS, compared to sham tDCS, resulted in significantly faster SRTs for incongruent stimuli.

Table 8.

Mean (SD) SRTs (seconds) for incongruent stimuli across baseline and stimulation sessions for the LIFG group for item data

	Baseline	Stimulation
Anodal	.594 (.035)	.551 (.044)
Sham	.605 (.030)	.613 (.033)

3.9.3 Analysis of RIFG congruent stimuli alone (black bars in Figure 6). The main effect of tDCS session (*F* (1, 286) = .048, p = .827) on SRTs was not significant. The interaction between tDCS session and tDCS type was not significant (*F* (1,286) = 1.130, p = .279). Inspection of means revealed SRT's were similar between sham and anodal (anodal mean = 0.397; SD = 0.163; sham mean = 0.410; SD = 0.162;) tDCS conditions at baseline and when tDCS was applied (anodal mean = 0.401, SD = 0.149; sham mean = 0.408; SD = 0.170).

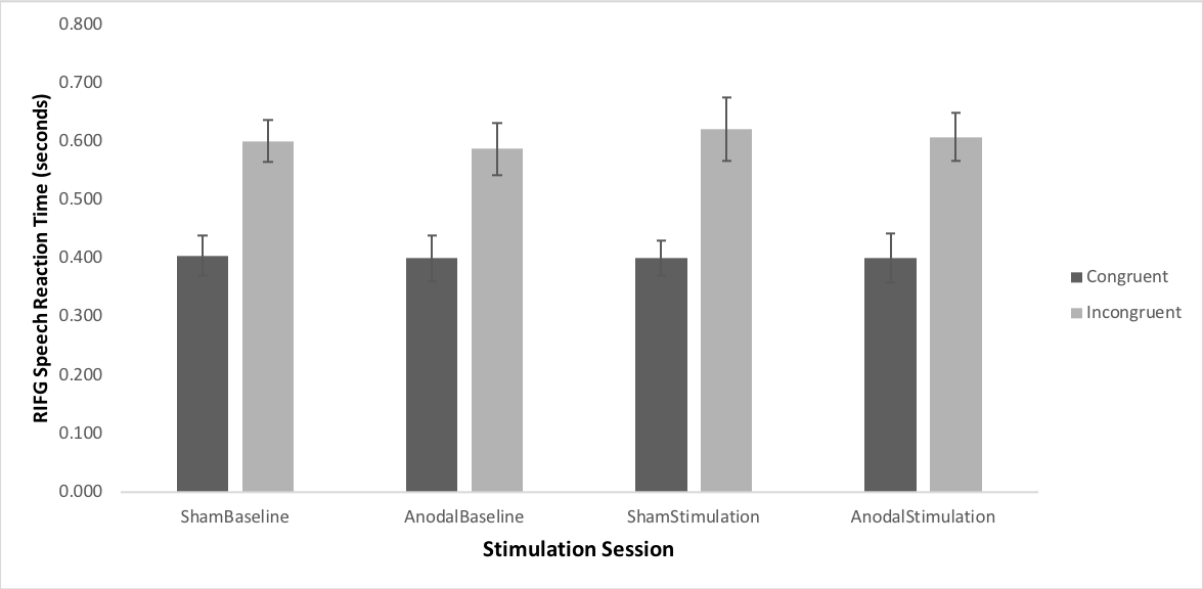

Figure 6. RIFG item mean SRTs (seconds) for congruent (black bar) and incongruent (grey bar) stimuli for sham and anodal stimulation separately for baseline and stimulation sessions. Error bars indicate +/- one standard error.

3.9.4 Analysis of RIFG incongruent stimuli alone (grey bars in Figure 6). The main effect of tDCS session (F (1, 70) = 1.690, p = .245) on SRTs was not significant. The interaction between tDCS session and tDCS type was not significant (F (1,70) = .0436, p = .983). Inspection of means revealed SRT's were similar between sham and anodal (anodal mean = .589; SD = .044; sham mean = .600; SD = .035) tDCS conditions at baseline and when tDCS was applied (anodal mean = .607, SD = .041; sham mean = .619; SD = .054).

3.9.5 Summary. Results showed anodal tDCS over the LIFG, compared to sham, resulted in significantly faster speech updating on incongruent trials. No significant effects for congruent stimuli were observed. Finally, no effects were observed for RIFG stimulation other than differences between congruent and incongruent stimuli.

3.10 Discussion

Study 1.1 explored the use of anodal tDCS for modulating speech preparation in a picture naming task in TS. Results confirmed our hypothesis, as there was a significant reduction of SRTs for anodal tDCS, compared to sham tDCS, for three syllable words. However, no significant reduction in SRTs occurred for one syllable words, suggesting that three syllable words, that required higher levels of speech preparation (compared to one syllable words) are needed to elicit effects of tDCS stimulation. This was followed up in Study 1.2 which explored the effect of anodal tDCS, compared to sham tDCS, on reformulation of speech motor plans during a primed picture naming task in TS. Results showed anodal tDCS over the LIFG, compared to sham, resulted in significantly faster speech plan reformulation on incongruent trials. Although there was some enhancement of SRTs on congruent trials during anodal tDCS, the difference in SRTs did not differ significantly between anodal and sham tDCS. RIFG tDCS did not significantly affect SRTs for either stimuli type. Overall, the results suggest that the anodal tDCS enhancement effect observed on incongruent trials was limited to when the LIFG, a crucial speech production region, was being stimulated.

3.10.1 Explanations of our results. The results in Study 1.1 contrast with the facilitation of SRTs of monosyllabic images reported by Holland et al. (2011). A possible explanation for this is that Holland et al. (2011) employed older individuals in their experiment, who were likely to display reduced cortical excitability. Stimulation with tDCS would therefore likely be more effective, compared to TS, as there is more room for improvement. As a result, an enhancement effect of tDCS is more likely to be induced compared to younger individuals who exhibit near-optimal levels of cortical excitability (Zimmerman et al., 2013). Whilst an effect of tDCS on three syllable naming latencies was found, this is likely to be greater in older individuals or other populations who display reduced cortical excitability.

Overall, the results in Study 1.1 are probably due to two factors: homeostatic mechanisms, which regulate neural activity to maintain optimal functioning in TS, and stimulus/task complexity. Research has demonstrated that longer durations of tDCS with higher intensities could possibly reverse the polarity of stimulation, with anodal stimulation leading to inhibition of neural regions rather than excitation (Nitsche et al., 2003). Homeostatic mechanisms are theorised to be activated to reduce excessive levels of neural activation, which in turn may nullify any effect of tDCS (Krause & Cohen Kadosh, 2014). Homeostatic mechanisms are particularly engaged when an excitatory stimulus, which increases cortical excitability (e.g. anodal tDCS), is applied immediately after an excitatory stimulus, leading to decreased cortical excitability (Bienenstock, Cooper & Munro, 1982). Furthermore, the direction of behavioural effects caused by brain stimulation (i.e., improving or disrupting performance) is difficult to predict. For instance, TMS across left temporal and inferior parietal regions has been shown to both enhance (Acheson et al., 2011; Mottaghy et al., 1999; Sparing et al., 2001; Töpper et al., 1998) and impede picture naming performance (Pobric et al., 2007; Schuhmann et al., 2012). Furthermore, the dissociation of performance improvement in response to anodal tDCS as opposed to performance decline in response to cathodal tDCS as documented for the motor cortex (Nitsche & Paulus, 2000) has been shown to be more complex for higher cognitive functions (Hill, Fitzgerald, & Hoy, 2016; Jacobson, Koslowsky & Lavidor, 2012). For example, Fertonani et al. (2010) found (descriptive) interference in picture naming from cathodal tDCS in their Experiment 1, but (descriptive) facilitation from cathodal tDCS in their Experiment 2. Therefore, tDCS effects may not be as straightforward in speech studies, partially explaining our results in Study 1.1.

It is possible that single sessions of tDCS cannot reliably modify processes and/or representations involved in picture naming tasks since they are so well established through years of practice (Woods et al., 2016). This may provide an explanation for the results observed in Study 1.1 as a picture naming task entails low demand, low complexity and producing high frequency words. Study 1.2 allowed us to quantify the speech preparation process as a whole by forcing participants to reformulate their speech production plan.

Research further shows that monosyllabic words engage the LIFG during speech in TS to a lesser extent compared to multisyllabic words (Sörös et al., 2006). With increasing word and syllable complexity, the activity and engagement of the LIFG in the task increases (Moser et al., 2009). This serves as a potential explanation for our results as tDCS effects depend on the engagement of a targeted region within the task (Fertonani & Miniussi, 2016; Miniussi et al., 2013; Peña-Gómez et al., 2012). It is therefore possible that the increased complexity in the three-syllable task led to increased LIFG engagement, which in turn led to enhanced effects of tDCS. These explanations are likely as whilst we observed no effect of tDCS on one syllable picture naming latencies, we observed a significant decrease in three syllable naming latencies. This suggests the effect of tDCS showed an ongoing interaction with the demands of the task. It is possible that a facilitation effect of tDCS would occur for both one and three syllable words if stimuli were in mixed blocks, possibly because it would maintain an elevated level of task demands.

The results in Study 1.2 are consistent with the behavioural findings of Mock et al. (2011, 2015). Participants used the primes presented to prepare their naming response, indicated by the difference in SRTs between congruent and incongruent trials. As we did not find an effect of tDCS on congruent trials, this can be interpreted as indicating that speech preparation took place prior to the onset of the target stimulus. Application of tDCS over a region involved in speech preparation (LIFG) probably led to enhanced excitability of this region. Consequently, due to research demonstrating the involvement of the LIFG in speech preparation, and enhancement of this region leading to faster speech response times (Holland et al., 2011, Long et al., 2016), it is likely that faster speech plan reformulation took place on incongruent trials resulting in enhanced SRT compared to sham tDCS. The significant facilitation of SRTs on incongruent trials indicated that tDCS could affect speech plan updating and speech preparation processes.

Alternatively, the LIFG plays a role in numerous cognitive processes other than speech-motor preparation. The LIFG has been shown to be involved in phonological processing and syllabification (Molnar-Szakacs et al., 2005; Papoutsi et al., 2009), involving

discrete unit sequencing (Gelfand & Bookheimer, 2003) and sublexical phonological processing that requires explicit attention (Burton et al., 2000; Zatorre et al., 1996). Research has also implicated the LIFG in verbal working memory tasks (Jonides et al., 1998; Sun et al., 2005). The above processes are also involved in the process of successful picture-naming and as such, may have been modulated by tDCS rather than speech-motor preparation processes. Hence, faster SRTs with anodal tDCS do not necessarily indicate improved function of speech-motor preparation and may indicate tDCS enhances other processes which support speech.

3.10.2 Do the results reflect possible linguistic modulation? Potential mechanisms for linguistic enhancement include Levelt's "mental syllabary" (Levelt et al., 1999). The mental syllabary is a hypothesised cortical centre (Brendel et al., 2011; Riecker et al., 2008) that stores precompiled speech units that are accessed during speech. The syllabary allows for the rapid retrieval of commonly produced and overlearned syllables. Therefore, tDCS may improve access and retrieval to the syllabary that then allows for more efficient articulation. For example, many studies have demonstrated that familiar words and words with high phonotactic probability are produced with shorter durations than unfamiliar words and words with low phonotactic probabilities (Munson, 2001; Munson et al., 2005; Wright, 1979). This illustrates a strong word-frequency effect purportedly due to the rapid access of the phonological code (Levelt, 1999). Consequently, one syllable words may not have been affected by tDCS due to the high efficiency with which this process operates. Three syllable words however, whilst the process is still efficient, require a greater level of processing. This allows "room for improvement" where tDCS may have facilitated processing resulting in improved naming latencies. It is also possible that this process accounts for the results in Study 1.2 where tDCS could have facilitated retrieval from the "mental syllabary". However, the mental syllabary theory does not account for the fact that all words across conditions were not affected by tDCS in our studies, which would occur if indeed mental syllabary was affected by tDCS.

Previous literature that has explored tDCS in speech and language studies has revealed that there is a great deal of variability in the effects observed, particularly within TS who receive a single session of tDCS (Neige et al., 2018). Some individuals show no effects on corticomotor excitability after tDCS and some individuals even show effects opposite to those predicted (Chew et al., 2015; Nitsche et al., 2004). Whilst some studies have shown picture naming and verbal fluency improvements in TS after tDCS (Holland et al., 2011; Lifshitz-Ben-Basat & Mashal, 2017; Price & Hamilton, 2015), other studies and meta-analyses suggest there is no reliable evidence for the effect of tDCS on speech and language modulation in TS (Horvath, Forte & Carter, 2014; Mancuso et al., 2016; Westwood, Olson, Miall, Nappo & Romani, 2016).

Some studies have been critical of the effects of tDCS on language and linguistic processes. Price, McAdams, Grossman and Hamilton (2015) also analysed tDCS effects on language and found a reliable modulation of task performance. However, effect sizes were small to moderate, and significant outcomes appeared to rely on large effect sizes from one study measuring fluency (Cattaneo et al., 2011) and one study measuring word learning (Flöel et al., 2008). Furthermore, Cattaneo et al. (2011) has proven difficult to replicate (Penolazzi et al., 2013; Vannorsdall et al., 2016). Horvath (2015) also pointed out that the offline effect for fluency tasks would become non-significant if some data from studies excluded by the authors were included and if some mistakes in effect size estimates were corrected. Consistent with this, Horvath, Forte and Carter (2015) analysed the effect of tDCS on language tasks and found no effect. However, the method used for this meta-analysis has been called into question (Antal et al., 2015; Chhatbar & Feng, 2015) due to its use of restrictive inclusion criteria and a small number of studies. More recently, Westwood and Romani (2017; 2018) found no effect of tDCS on language production performance across production and reading tasks. Due to the size and inconsistency of tDCS effects on language reported within literature, it is unlikely that tDCS induced language enhancement could account for the results observed in our studies.

3.10.3 Summary of results. Overall, anodal tDCS resulted in a significant reduction of SRTs for three syllable words on our picture naming task compared to sham tDCS (Study 1.1). SRTs for reformulating 3 syllable speech plans were quicker under anodal, compared to sham, tDCS (Study 1.2). Crucially, anodal tDCS did not affect SRTs on congruent trials. The results suggest that tDCS did not have an effect on the linguistic elements of speech preparation. This is consistent with research showing production of monosyllabic words on a picture naming task is an overlearned and oversimplified task lacking the complexity required to sufficiently engage the LIFG (Sörös et al., 2006). In addition, the effects of tDCS are largely dependent on engagement of the targeted region in a task itself and task/stimuli complexity to produce effects (Bikson & Rahman, 2013; Stagg et al., 2011). A significant modulation was observed on incongruent trials, where speech motor preparation required reformulation. Research shows disruption of the LIFG leads to slowing of speech timing and vocal responses (Long et al., 2016). It is possible, therefore, that enhancement of LIFG activity could result in quicker speech timing vocal responses and in our study, SRTs. As the production of three syllable words on incongruent trials requires greater speech preparation, and greater recruitment of the LIFG, it is likely that speech preparation was enhanced by anodal tDCS interacting with ongoing task-related activity. Therefore, the effects observed in the studies in this chapter were probably a result of increased requirement for, and complexity of, speech preparation processes.

3.10.4 Limitations and future research. One limitation of both studies is that same stimuli were repeated across all blocks of the experiment, albeit in different random orders. The repetition of stimuli may have led to familiarity and speech motor priming. This may have influenced speed of naming latencies. However, as no effect was observed with congruent trials, it is unlikely familiarity and priming had an effect on naming latencies. This could easily be rectified in future research by using different sets of stimuli, with similar difficulties, per condition.

A further limitation of our studies is the sample size used. Although our samples were large enough to reveal effects in both studies, it may be the case that the sample size was too small to detect a small effect for one syllable words. The ability to detect differences which exist would be limited when statistical power is low. Our studies had small overall sample sizes (27-30 participants). Low power leads to a reduced chance of finding a significant effect (Button et al., 2013; Minarik et al., 2016). However, similar sample sizes were employed in most of the tDCS studies to date (Elsner et al., 2015). A sample of 25 participants or more per group is required for a between group design to have sufficient power (Guerra et al. 2017).

In addition, we did not ask participants if they felt they were receiving real or sham stimulation, as this may affect people's performance (Horvath et al., 2014). None of the present participants had received tDCS previously. Some experienced participants might be able to differentiate sensory differences (itching, tingling or burning feelings) between active and sham stimulation. This leads to ineffective blinding, causing expectation effects (Davis et al., 2013), which may affect tDCS outcomes (Rabipour, Wu, Davidson & Iacoboni, 2018).

Finally, particularly for experiment 1.2, the lack of a baseline makes it difficult to determine what "faster" or "slower" actually means. Although a baseline condition was included, this baseline was performance without stimulation. Hence, due to counterbalancing, some participants completed the with tDCS session first whilst others completed the without tDCS session first. Practice effects may have therefore influenced performance across sessions.

Further research is likely required to examine modulation of speech production using tDCS in tasks which can separate linguistic and motoric processes.

3.10.5 Conclusion. Overall, our results demonstrated that anodal tDCS over the LIFG can modulate speech preparation processes in TS particularly for complex material. This was demonstrated by anodal tDCS induced picture naming latency reduction when naming three syllable words and picture naming trials preceded by incongruent (with the

target name) primes. Our findings provide proof of principle that anodal tDCS over the LIFG can be used to modulate speech preparation processes. However, picture naming is a simplistic measure of speech production with relatively low complexity (due to 1-3 syllable production), and possible influences of linguistic processes such as word retrieval. In order to further examine the potential of tDCS to modulate speech processes, tDCS over the LIFG must be explored within a complex connected speech task which may elucidate effects of LIFG tDCS on articulation.

Chapter 4: Using tDCS to modulate speech articulation during tongue twister repetition.

4.1 Introduction

In Chapter 3 speech preparation was modulated using anodal tDCS in two picture naming tasks in TS. The first study in that chapter revealed a significant reduction of SRTs for anodal tDCS, compared to sham tDCS, for three syllables, but not one syllable, words. These findings suggested that a conventional picture naming task is probably too simple for assessing speech preparation since complexity could explain the difference between findings on one and three syllable words. The second study in Chapter 3 explored the effect of LIFG anodal tDCS on speech plan formulation and updating. Congruent and incongruent primes preceded the picture to be named. The primes allowed speech responses to be prepared when the prime and picture were congruent but not when the prime and picture were incongruent. SRTs differed between congruent and incongruent stimuli that allowed/did not allow planning, respectively, for anodal and sham stimulation both in sessions where tDCS was and was not received. There was no effect of anodal tDCS on picture naming latencies on congruent trials, but there was a significant effect of anodal tDCS on SRTs in the more difficult incongruent trials. The results therefore suggested anodal tDCS over the LIFG can enhance speech preparation, indicated by faster updating of a speech plan, under anodal tDCS compared to sham tDCS. Our findings provided proof of principle that anodal tDCS can be used to modulate speech preparation processes and such neurostimulation is worth pursuing in experiments with PWS. However, picture naming tasks provide a simple measure of speech production with low complexity, unlike more demanding connected speech. They may also be influenced by linguistic processes such as working memory. Therefore, before examining tDCS with PWS, a study is reported in which anodal tDCS was applied during a connected speech task, which involved tongue twister repetition (by definition, difficult to produce) to improve articulation processes.

To date few studies have examined the effect of applying tDCS to the LIFG and seeing whether this affects speech motor processes, particularly on articulation. Chesters et

al. (2017) examined speech motor learning in TS during complex non-word repetition practice and assessed whether tDCS enhanced online and offline processes that contribute to speech motor learning. The results showed that 20-minute practice improved non-word repetition and that tDCS improved this online learning in the first session. tDCS improved within-day offline learning (during 1 hour after practice) in the second session but had no effect on between-day offline learning (from 1 to 24 hours after practice) in either session. No differences were found in the effectiveness of different stimulation protocols, indicating that neither intensity (1 vs. 2mA) nor placement of the cathode (right supraorbital ridge vs. IFG had any effect. The results demonstrated that anodal tDCS applied to the LIFG affected online and within-day, but not between-day, offline components of speech motor learning.

Two previous studies have explored the effect of applying tDCS to LIFG on speech articulation processes using tongue twister stimuli (Fiori, Cipollari, Caltagirone & Marangolo, 2014; Wong, Chan, Ng & Zhu, 2018). Tongue twisters were used in preference to normal sentences because they use words with similar phonetic structure that makes them difficult to articulate (Wong et al., 2018). Due to the articulatory complexity of tongue twisters compared to conventional speech, repetition of these stimuli occasionally leads to insertions, deletions, or substitutions of phonemes (Dell, 1986; McMillian & Corley, 2010; Shattuck-Hufnagel & Klatt, 1979).

Fiori et al. (2014) assessed the effect of anodal tDCS on tongue twister repetition in a group of TS 1 hour before, during and 1 hour after tDCS. Speed of tongue twister repetition was assessed with verbal response times (VRTs; stimulus offset to response offset). During anodal tDCS (2ma for 20 minutes) of the LIFG accuracy and speed of articulating 34 Italian tongue twisters improved compared to either cathodal or sham tDCS. Furthermore, cathodal stimulation also reduced accuracy and speed of tongue twister articulation during tDCS. No effects were observed pre and post stimulation. In a study by Wong, Chan, Ng and Zhu (2018), thirty TS (native Cantonese adult speakers) repeated tongue twisters immediately before, immediately after and 4 hours after anodal (2ma, 20 minutes) or sham tDCS over the LIFG. No significant differences between the anodal tDCS and sham tDCS groups on either

speech rate or response accuracy were observed. The difference in results between Wong et al.'s (2018) and Fiori et al.'s (2014) studies are likely to be due to several methodological differences. The studies differed in their methods of stimulus presentation (visual vs. auditory), the behavioural tasks (reading tongue twisters aloud vs. repetition of tongue twisters), and outcome measures used (speech rate vs. VRT). VRT is a measure of the time from offset of the stimulus to end of the articulation of the tongue twister and differs from SRT used in the studies in Chapter 3. The outcome measure used by Wong et al. (2018) was notably different from typical measures of speech performance, as speech rate was calculated by dividing the total number of words produced by duration (in seconds) from onset to the offset of the participant's response. This method was employed because Cantonese words are predominantly monosyllabic (Bauer & Benedict, 1997).

Given the significant effects of tDCS on articulatory performance reported by Fiori et al (2014), we attempted to replicate their findings with English tongue-twisters. Advantages in using tongue twisters are that this is closer to spontaneous speech than are tasks like picture naming and spontaneous speech is a mode that PWS have difficulty with. The hypotheses were based on the findings of Fiori et al. (2014) and our findings in Chapter 3, which suggested that tDCS may be more effective with complex stimuli. Similarly to Fiori et al. (2014), we examined VRTs in this study to capture the effect of LIFG tDCS on the whole articulation process, rather than only the speech preparation process as in Chapter 3. Furthermore, we employed a control stimulation site as in Chapter 3 to ensure specificity of effects (Fiori et al., 2014 did not use a control site). The site used here was the RIFG again. It was hypothesised that a) anodal tDCS over the LIFG would lead to significantly faster tongue twister VRTs compared to sham and cathodal tDCS during, but not pre or post stimulation; b) cathodal tDCS over the LIFG would result in significantly slower tongue twister VRTs compared to anodal tDCS and sham during, but not pre or post stimulation; and c) tDCS over the RIFG would not result in significant changes to VRTs compared to any time point with any form of stimulation.

4.2 Method

4.2.1 Participants. One sample of 30 participants (15 male, 15 female) was recruited from the UCL SONA participant recruitment system. Participants were assigned to one of three stimulation groups, with ten participants per group: anodal (M age =20.0, SD=0.93), cathodal (M age =20.88, SD=2.23) and sham (M age =19.63, SD=0.74). A second sample of 30 participants (17 male, 13 female) was assigned to the RIFG group and ten each received one of the aforementioned forms of tDCS stimulation (anodal mean age = 24.3, SD = 5.05; sham mean age = 25.8, SD = 7.98; cathodal mean age = 22.1, SD = 4.28).

Inclusion criteria were: English as first language; right handed; no history of chronic or acute neurologic, psychiatric, or medical conditions; no speech, language or uncorrected sensory impairment; no family history of epilepsy; not on acute or chronic medication in the six months prior to testing. All participants reported normal hearing and had normal or corrected vision. All participants self-reported they had no speech or language disorder. Ethical approval was granted by the UCL Doctoral School Ethics Committee. Informed consent was obtained from participants.

4.2.2 Design. Participants attended for three sessions (one hour before stimulation, stimulation session and one hour after stimulation). The study was a double blind, 2x3x3 repeated measures design. The dependent variable was VRT (measured from stimulus offset to response offset) and the independent variable was the stimulation condition (sham, anodal or cathodal tDCS). Stimuli were delivered in a randomised order for every session, and tDCS sessions were counterbalanced.

4.2.3 Materials. A pool of 38 English tongue-twisters was collected from online sources. Versions of these were recorded by a fluent male speaker using Audacity software and a Yeti USB microphone. Participants listened to the audio recording of the tongue twisters via headphones.

PsychoPy software (Peirce, 2007) was used for stimulus presentation, and participants' speech was recorded using Audacity software. A Yeti USB microphone was positioned 20 cm from each participant's mouth and approximately 20 degrees from vertical for recording responses.

4.2.4 Stimulation. The tDCS stimulation procedure described in Chapter 3 Study 1.2 was used again in this experiment, including the control stimulation site (RIFG). The anodal electrode was placed over F6 according to the EEG 10-20 system, with the reference electrode was positioned over the contralateral frontopolar cortex. Stimulation was delivered for 20 minutes (2 mA) within the 'During' time point of our study.

4.2.5 Procedure. Participants were allocated to anodal, cathodal or sham stimulation at random prior to recruitment. Blind allocation to stimulation conditions prevented allocation bias. Participants completed six practice tongue twister trials, followed by the experimental trials. The screen was blank throughout the experimental trials. On each trial, a 500-ms warning tone alerted the participant that a tongue-twister would be played 2 seconds later. After the tongue-twister had finished playing there was a 15-s silence period in which participants repeated the tongue twister as quickly and as accurately as possible. The 38 tongue-twisters were presented in random orders across sessions. The one-hour break between sessions was used as a tDCS washout period as in Fiori et al. (2014). The procedure was identical in each session.

4.2.6 Data analysis. Inferential tests used SPSS 22.0. VRTs were measured manually to ensure accuracy. We examined VRTs in this study, as in Fiori et al. (2014), to capture the effect of tDCS on the whole articulation process, rather than only the speech preparation process measured by SRT as used in Chapter 3. Audio files were imported into STS, and the beginning and end of utterances were annotated manually onto the audio waveforms. VRTs were calculated as the duration between offset of the tongue twister

stimulus and offset of the participant's response. For completeness and comparability, speech rate (words per second), as used by Wong et al. (2018), was calculated by dividing the total number of words produced by duration (in seconds) from onset to the offset of the participant's response. Speech accuracy was calculated as the percentage of correctly produced trials within each condition. Mixed model ANOVAs were used with the factors time (before, during, after stimulation, within group) and stimulation type (anodal, cathodal, sham, between group). Significant effects were followed up with Independent Samples T-Test's.

4.3 Results

4.3.1 VRT Analysis. For the LIFG (Figure 7), there was a significant effect of time ($F(2, 54)=20.530$, $p<.001$), indicating participant VRTs reduced with each session, from pre (mean: 3.417, SE: .065) to during (mean: 3.198, SE: .073) to post (mean: 3.162, SE: .075) stimulation. A significant interaction between time and the type of stimulation ($F(4, 54)=3.038$, $p=0.025$) was observed, indicating the improvement in VRTs across sessions was modulated by tDCS stimulation. For the RIFG (Figure 8), there was no significant effect of time ($F(2, 54)=1.348$, $p = .268$) and no significant interaction between time and the type of stimulation ($F(4, 54)=.029$, $p=.997$). Independent samples t-tests were then conducted to assess the effect of tDCS on VRTs across sessions for both the LIFG and RIFG. Comparisons were made between anodal and sham stimulation, anodal and cathodal stimulation, and sham and cathodal stimulation for all time points across both the LIFG and RIFG. As illustrated in Tables 9 (table of means) and 10 (table of statistical estimates), LIFG anodal tDCS (mean: 2.947, SD: 0.385) resulted in significantly ($p = .047$) quicker VRTs compared to sham (mean: 3.342, SD: 0.439) and cathodal (mean: 3.305, SD: 0.367) tDCS when stimulation was applied. No other significant effects were observed across the LIFG and RIFG across sessions and stimulation types.

Table 9.

Mean VRTs (SE) in seconds for Sham, Anodal and Cathodal stimulation groups across pre, during and post-tDCS sessions for the LIFG and RIFG

	Sham	Anodal	Cathodal
LIFG Pre	3.454 (.106)	3.376(.123)	3.419 (.108)
LIFG During	3.342 (.138)	2.947 (.121)	3.306 (.116)
LIFG Post	3.271 (.137)	3.000 (.144)	3.216 (.106)
RIFG Pre	3.399 (.095)	3.469 (.118)	3.366 (.112)
RIFG During	3.322 (.146)	3.393 (.142)	3.298 (.097)
RIFG Post	3.260 (.140)	3.301 (.133)	3.241 (.133)

Table 10.

Results of Independent Samples t tests comparing VRTs across stimulation conditions and time points for the LIFG and RIFG (df = 18 throughout)

	Sham vs. Cathodal		Anodal vs. Cathodal		Sham vs. Anodal	
	t	p value	T	p value	t	p value
LIFG Pre	.236	.816	-.262	.796	.484	.634
LIFG During	.200	.843	-2.129	.047	-2.137	.047
LIFG Post	.314	.757	-1.206	.243	1.357	.192
RIFG Pre	.219	.829	.626	.539	-.461	.651
RIFG During	.136	.894	.552	.588	-.349	.731
RIFG Post	.096	.924	.313	.758	-.209	.837

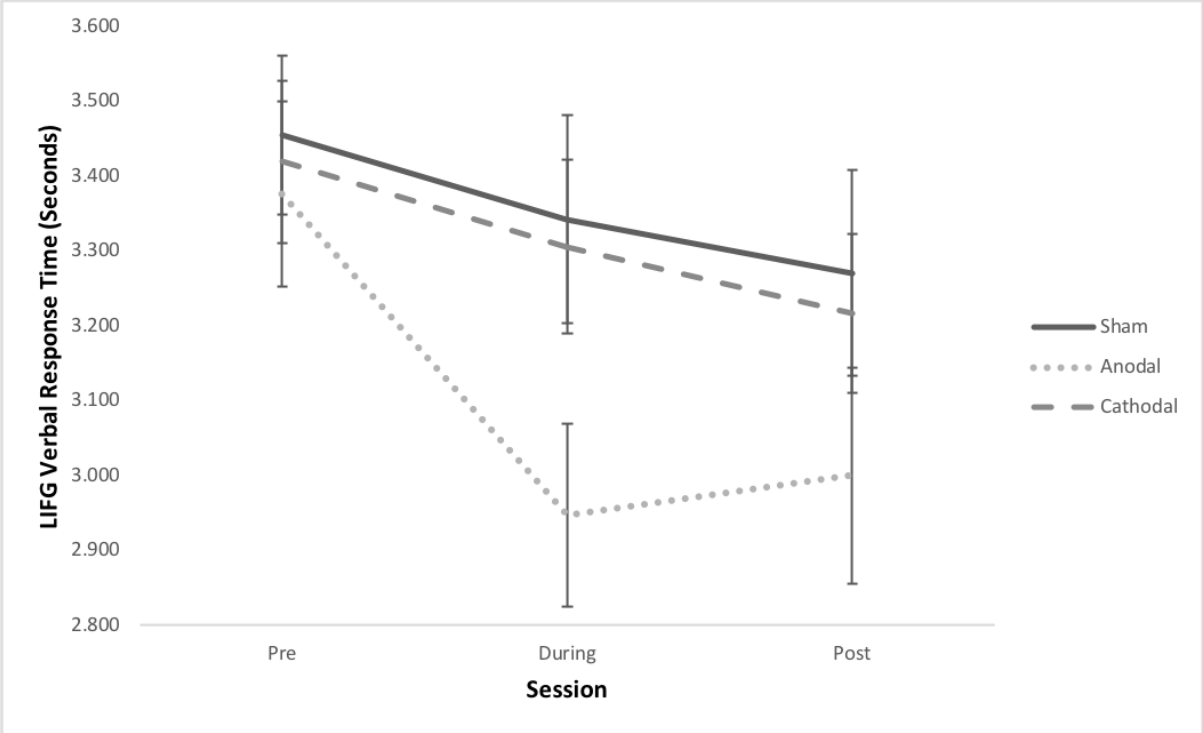

Figure 7. Mean VRT in seconds for the LIFG condition across the three-time points. Error bars indicate +/- one standard error.

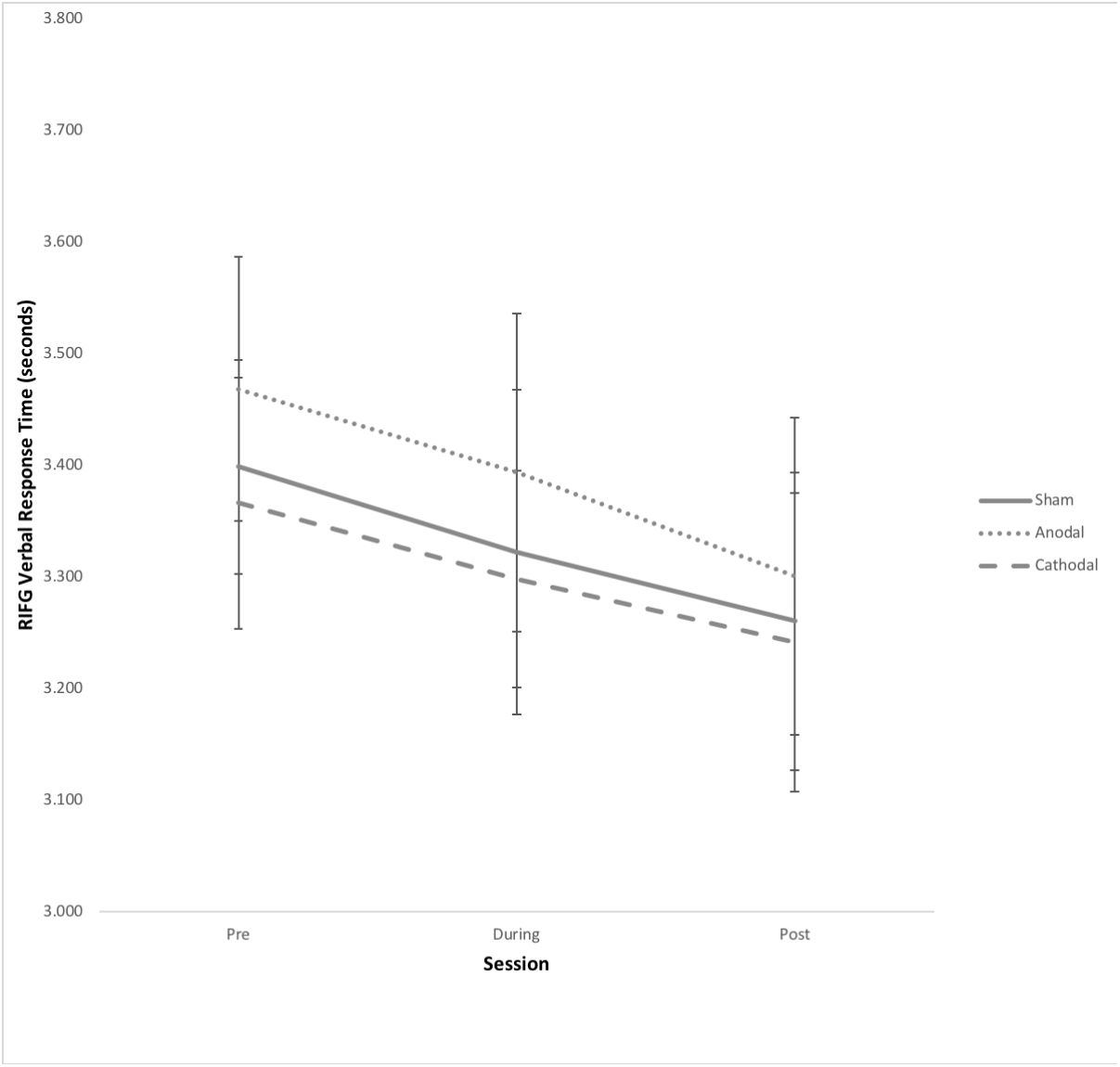

Figure 8. Mean VRTs in seconds for the RIFG condition across the three-time points. Error bars indicate +/- one standard error.

4.3.2 Speech Rate Analysis. Mixed ANOVAs were conducted to assess the effect of tDCS on speech rate, with factors of time (before, during, after stimulation, within group) and stimulation type (anodal, cathodal, sham, between group).

For the LIFG (Figure 9), there was a significant main effect of time ($F(2, 54)=15.622$, $p<0.001$), indicating participant speech rate improved with each session, from pre (mean: .416, SE: .009) to during (mean: .387, SE: .010) to post (mean: .381, SE: .009) stimulation. There was no significant interaction between time and the type of stimulation ($F(4,$

54)=1.922, p=.136), indicating the improvement in VRTs across sessions was not modulated by tDCS stimulation. For the RIFG (Figure 10), there was no significant effect of time (F(2, 54)=1.722, p = .188) and no significant interaction between time and the type of stimulation (F(4, 54)=.110, p=.967). Subsequent independent samples t-tests (Table 11 for means and Table 12 for statistical values) showed no significant effects across the LIFG and RIFG across sessions and stimulation types.

Table 11.

Mean speech rate (SE) in words per second for Sham, Anodal and Cathodal stimulation groups across pre, during and post-tDCS sessions for the LIFG and RIFG

	Sham	Anodal	Cathodal
LIFG Pre	.424 (.015)	.412 (.015)	.411 (.014)
LIFG During	.403 (.019)	.361 (.016)	.397 (.015)
LIFG Post	.387 (.014)	.357 (.015)	.395 (.014)
RIFG Pre	.409 (.011)	.436 (.010)	.415 (.012)
RIFG During	.407 (.011)	.421 (.010)	.409 (.013)
RIFG Post	.396 (.015)	.411 (.021)	.400 (.015)

Table 12.

Results of Independent Samples t tests comparing speech rate across stimulation conditions and time points for the LIFG and RIFG (df = 18 throughout)

	Sham vs. Cathodal		Anodal vs. Cathodal		Sham vs. Anodal	
	t	p value	T	p value	t	p value
LIFG Pre	.604	.553	.028	.978	.574	.573
LIFG During	.205	.839	-1.645	.117	1.645	.117
LIFG Post	-.328	.746	-1.768	.094	1.463	.161
RIFG Pre	-.377	.711	1.271	.220	-1.738	.099
RIFG During	-.125	.902	.736	.471	-.922	.369
RIFG Post	-.178	.860	.387	.703	-.545	.592

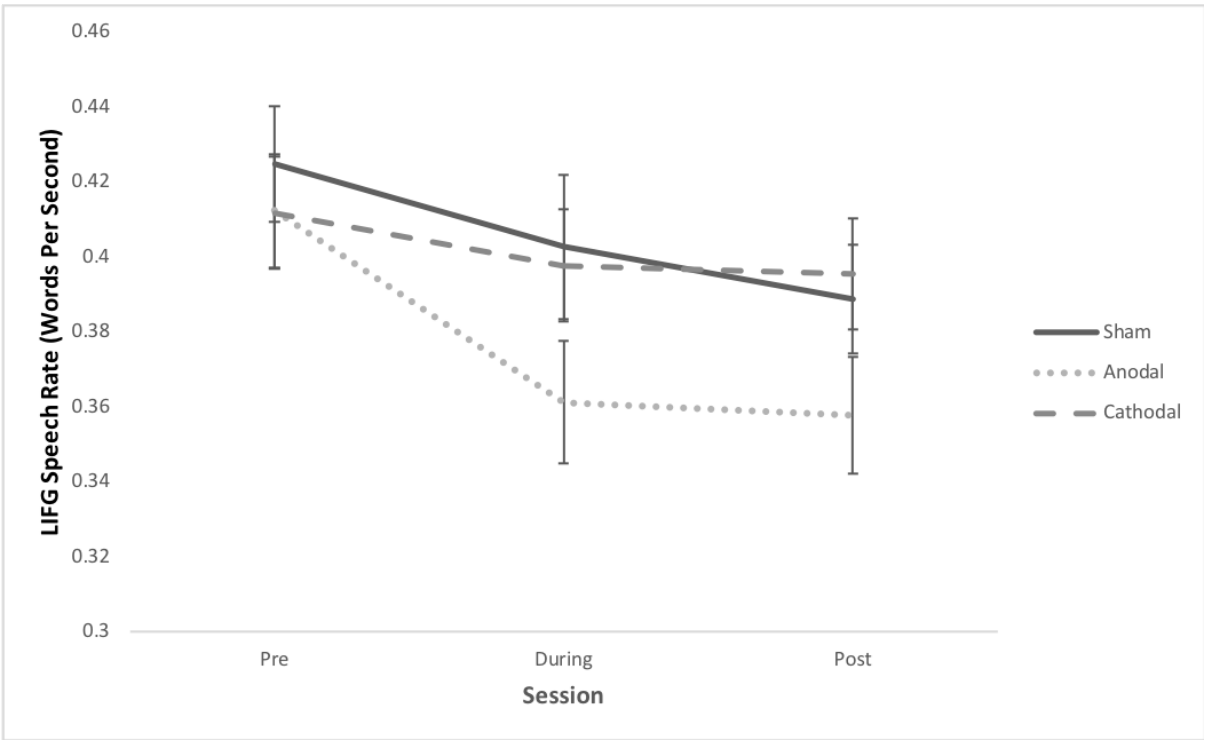

Figure 9. Mean speech rate in words per second for the LIFG condition across the three-time points. Error bars indicate +/- one standard error.

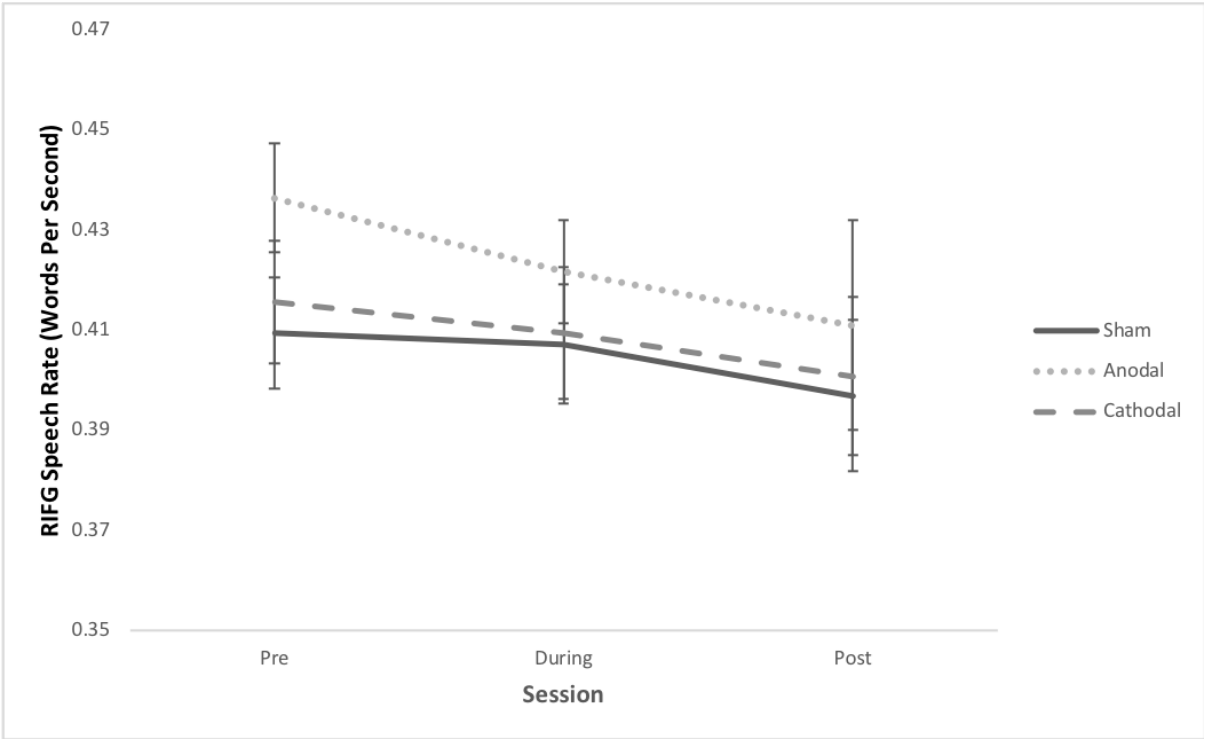

Figure 10. Mean speech rate in words per second for the RIFG condition across the three-time points. Error bars indicate +/- one standard error.

4.3.3 Accuracy Analysis. For the LIFG (Figure 11), there was a significant main effect of time ($F(2, 54)=42.311$, $p<.001$), indicating tongue twister repetition percentage accuracy increased with each session, from pre (mean: 63.86%, SE: 2.494) to during (mean: 71.57%, SE: 2.296) to post (mean: 74.82%, SE: 2.699) stimulation. No significant interaction between time and the type of stimulation ($F(4, 54)=1.827$, $p= .145$) was observed, indicating tongue twister repetition percentage accuracy was not modulated by LIFG tDCS stimulation across sessions. Similarly, for the RIFG (Figure 12), there was a significant main effect of time ($F(2, 54)=32.495$, $p<.001$), indicating tongue twister repetition percentage accuracy increased with each session, from pre (mean: 63.77%, SE: 2.319) to during (mean: 68.77%, SE: 2.149) to post (mean: 73.509, SE: 2.380) stimulation. No significant interaction between time and the type of stimulation ($F(4, 54)=.364$, $p= .785$) was observed, indicating tongue twister repetition percentage accuracy was not modulated by RIFG tDCS stimulation across sessions. Subsequent independent samples t-tests (Table 13 for means and Table 14 for statistical values) showed no significant effects across the LIFG and RIFG across sessions and stimulation types.

Table 13.

Tongue twister repetition percentage accuracy (SE) for Sham, Anodal and Cathodal stimulation groups across pre, during and post-tDCS sessions for the LIFG and RIFG

	Sham	Anodal	Cathodal
LIFG Pre	65.53% (4.251)	62.63% (4.721)	63.42% (3.951)
LIFG During	70.00% (3.642)	71.05% (4.675)	73.68% (3.509)
LIFG Post	73.68% (5.160)	72.37% (5.368)	78.42% (3.182)
RIFG Pre	66.32% (4.504)	60.79% (3.873)	64.21% (3.621)
RIFG During	69.47% (3.807)	66.05% (4.429)	70.79% (2.731)
RIFG Post	75.53% (4.542)	70.26% (4.869)	74.74% (2.578)

Table 14.

Results of Independent Samples t tests comparing tongue twister repetition percentage accuracy across stimulation conditions and time points for the LIFG and RIFG (df = 18 throughout)

	Sham vs. Cathodal		Anodal vs. Cathodal		Sham vs. Anodal	
	t	p value	T	p value	t	p value
LIFG Pre	-.128	.899	.363	.721	.456	.654
LIFG During	-.450	.658	-.728	.476	-.178	.861
LIFG Post	-.970	.345	-.781	.445	.177	.862
RIFG Pre	-.645	.527	.364	.720	-.930	.364
RIFG During	-.910	.375	-.281	.782	.586	.565
RIFG Post	-.812	.427	.151	.882	.790	.440

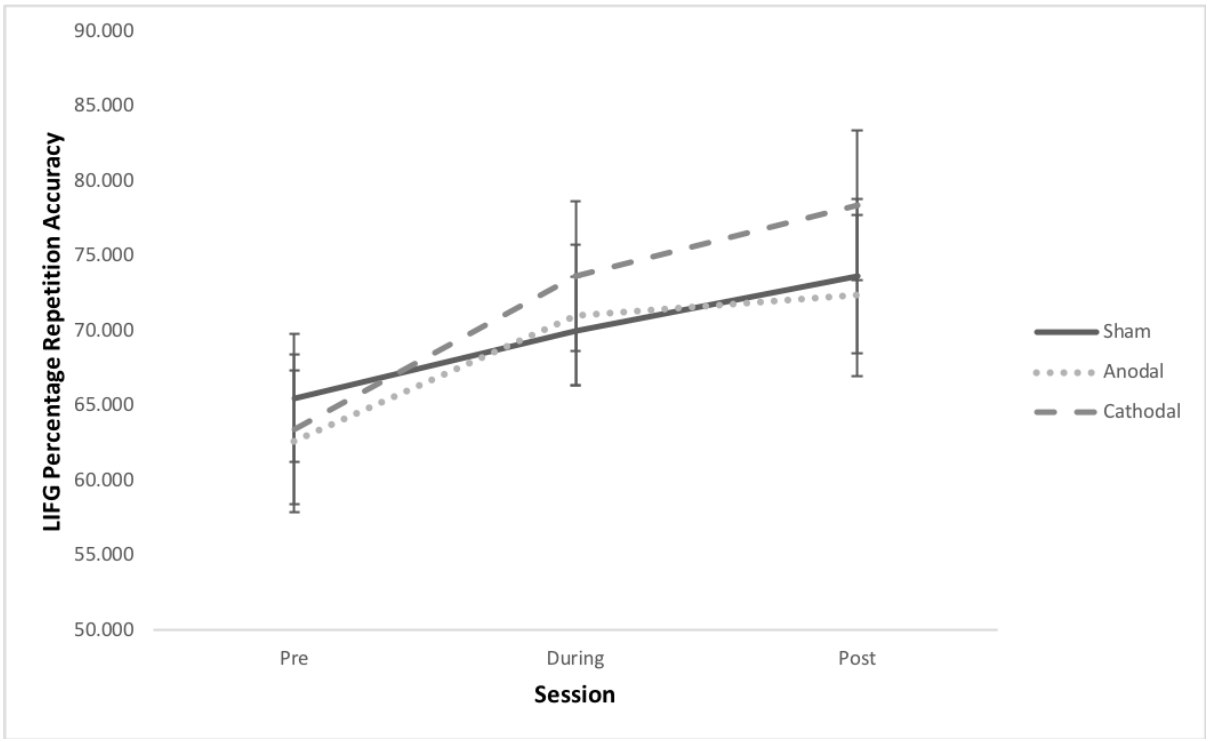

Figure 11. Tongue twister repetition percentage accuracy for the LIFG condition across the three-time points. Error bars indicate +/- one standard error.

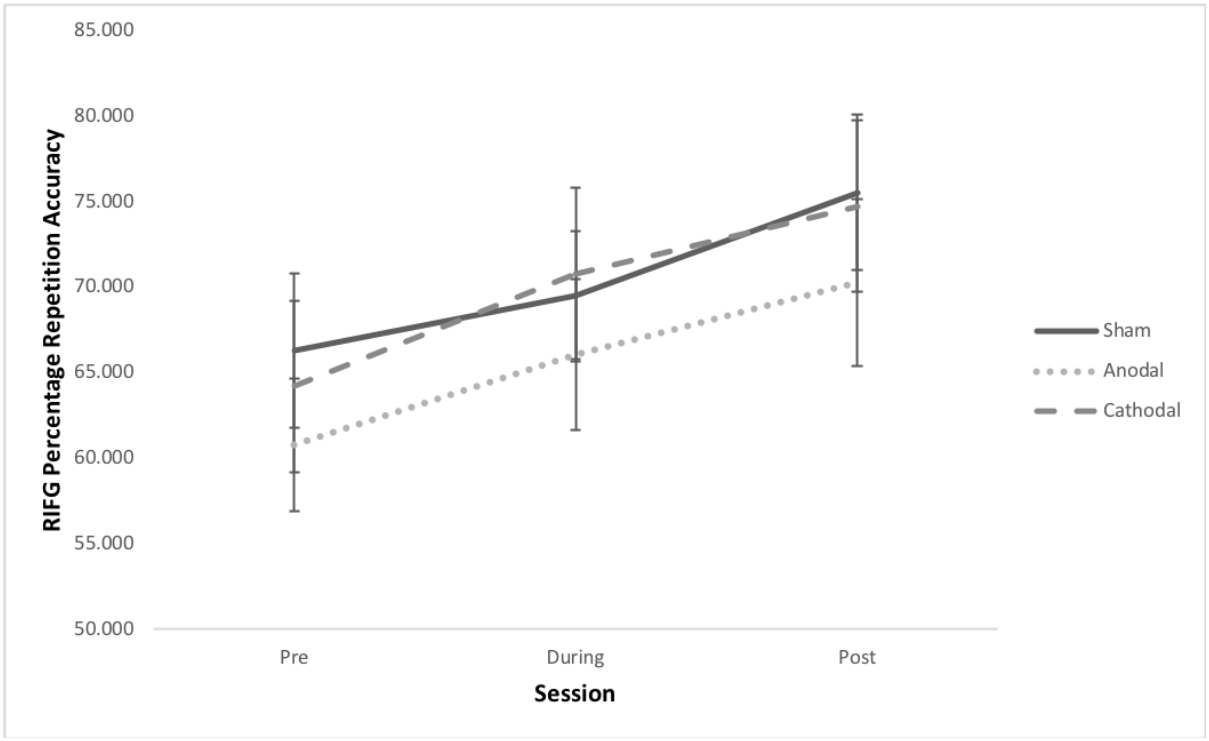

Figure 12. Tongue twister repetition percentage accuracy for the RIFG condition across the three-time points. Error bars indicate +/- one standard error.

4.3.4 Summary. Overall, results demonstrate anodal tDCS, compared to sham and cathodal tDCS, reduced VRTs for tongue-twisters during, but not pre or post stimulation. We did not observe an effect for cathodal stimulation compared to anodal and sham tDCS. We also did not observe any effects for stimulation of our RIFG control site. Finally, we did not observe any effects of LIFG or RIFG tDCS on speech rate or tongue twister repetition percentage accuracy.

4.4 Discussion

This study attempted to modulate speech articulation processes in TS. Participants repeated tongue twister stimuli one hour before, during and one hour after either anodal, cathodal or sham tDCS for both groups over the LIFG and RIFG. The results revealed that anodal tDCS, compared to sham and cathodal tDCS, reduced time to complete tongue-twisters during, but not pre or post stimulation. Results therefore supported our first hypothesis. No effect was observed for cathodal stimulation compared to anodal and sham tDCS, thus our second hypothesis was rejected. We did not observe any effects for stimulation of our RIFG control site, so our third hypothesis was supported.

4.4.1 Comparison to previous tongue twister studies in TS. The results are partially consistent with Fiori et al. (2014) who found significantly quicker tongue twister VRTs during anodal tDCS over the LIFG during stimulation, but not pre or post stimulation. However, Fiori et al. (2014) also observed a slowing down of tongue twister repetition VRTs in response to cathodal tDCS, which did not happen in the current study. The lack of significant differences as a result of cathodal tDCS was unexpected, but unsurprising, as research has shown that cathodal tDCS effects are highly inconsistent across cognitive tasks and may be limited to populations with impaired or diminished (e.g. older individuals) cortical excitability (Woods et al., 2016). In addition, our accuracy analysis did not show an effect of tDCS on tongue twister naming accuracy, which it did in the study reported by Fiori et al (2014).

The results of our study are not consistent with the findings of Wong et al. (2018) when using VRT, time from stimulus offset to response offset (Fiori et al., 2014), to assess the effect of tDCS on tongue twister repetition. However, results are consistent with Wong et al. (2018) when using their method of calculating speech rate to assess tongue twister repetition performance, as tDCS was found not to affect tongue twister repetition speech rate. Such a discrepancy in findings suggests methodological factors play a crucial role in elucidating differences in task performance. Overall, our study had several methodological differences to Wong et al. (2018). For example, the timing of data collection in relation to stimulation varied between Wong et al. (2018) and our study. Wong et al. (2018) assessed performance pre-stimulation, immediately after and 4 h after stimulation, whereas we assessed performance 1 hour before stimulation, during stimulation and 1 hour after stimulation. Wong et al., (2014) worked on Mandarin whereas our study was on English. Due to the substantial methodological differences, our results cannot be compared directly to Wong et al. (2018). However, the findings confirm the anodal tDCS effect that Fiori et al. (2014) reported.

4.4.2 Task demands and difficulty are essential for producing tDCS effects. A plausible explanation for our tongue twister finding is that difficult tasks are needed to observe effects of tDCS, consistent with our findings with three syllable words in Chapter 3 (Study 1.2). Previous research has suggested the effects of tDCS are highly dependent on task-specific neural activity and behavioural demands (Bestmann et al., 2015; Bikson & Rahman, 2013; Miniussi et al., 2013; Pirulli et al., 2014).

Research supports this conclusion as increases in speech sequence complexity are associated with increased LIFG activity. For example, participants in Bohland and Guenther's (2006) study spoke or prepared to speak non-word sequences. The LIFG has been associated with the Speech Sound Map component of the DIVA model (Guenther et al., 2006). A prediction of the model, which suggests that Speech Sound Map cells read out motor plans for well-learned speech "chunks," is that there should be additional activity when

multiple chunks are activated. Because production of complex sequences requires the activation of multiple speech sound map cells, one would expect to observe additional activity with fMRI. The tongue twisters used in the current study therefore probably resulted in high LIFG engagement, which interacted with the anodal tDCS stimulation, resulting in articulation facilitation and faster VRT's. Another mechanism by which our effects may have occurred is through efficient transfer of speech motor plans across the speech motor network. As the LIFG is particularly involved in speech motor planning (Flinker et al., 2015), tDCS of this region may have led to increased cortical excitability of the LIFG and interconnected regions, resulting in increased efficiency of speech motor plan formulation and transfer of this plan to the orofacial motor cortex, enabling enhanced execution and speech production (Flinker et al., 2005; Hickok & Poeppel, 2007; Price, 2010).

Research has shown that the effects of tDCS depend on task demands. Simione, Fregni and Green (2018) explored the effect of tDCS on jaw movements and task performance during tasks that varied in their level of complexity. TS completed speech, maximum syllable repetition, and chewing tasks whilst their jaw movements were recorded using 3D optical motion capture during 2mA of bilateral sham, anodal, and cathodal tDCS over the sensorimotor cortex. It was found that compared to the sham condition, jaw displacements (size, speed and duration of movement) during speech and syllable repetition were smaller during anodal stimulation, but larger during cathodal stimulation for syllable repetition and chewing. There were no effects of anodal tDCS during chewing. Anodal stimulation therefore resulted in improved biomechanical efficiency for speech and syllable repetition whereas cathodal stimulation resulted in reduced biomechanical efficiency for syllable repetition and chewing. Speech was considered to be the most complex task, followed by syllable repetition, with chewing being considered an automatic and low complexity movement. These results therefore demonstrated that the effects of tDCS depend on task demands, with higher task demands from speech and syllable repetition tasks resulting in greater tDCS effects.

Previous research has therefore shown that a task must engage the targeted region and be sufficiently complex to modulate cortical excitability using tDCS (Simione et al., 2018; Stagg & Nitsche, 2011). Therefore, tongue twisters being complex sequences, probably resulted in high LIFG engagement within our task and consequently interacted with the tDCS to produce improvements in speech articulation performance.

4.4.3 Cognitive mechanisms involved in tongue twister repetition. The speech production task in our study involved cognitive functions other than those involved in planning and articulation. During word repetition, the verbal material is kept in a working memory store using an 'articulatory loop'. The articulatory loop includes a phonological store and a subvocal articulatory rehearsal process capable of refreshing the word memory trace to prevent its decay (Baddeley & Hitch, 1994). Research has demonstrated the involvement of the LIFG within this rehearsal process (Baddeley, 2010; Paulesu et al., 1993; Romero et al., 2006; Trost & Gruber, 2012).

Research is not consistent with respect to the effect of tDCS on working memory in TS. Some studies have suggested that tDCS has a small but positive effect on both accuracy and reaction times (Hill et al., 2016), while others have suggested positive effects only in reaction times (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016), while others still have suggested no effect at all (Westwood & Romani, 2018). A comprehensive review of tDCS studies found small to null effects across reaction times and accuracy scores (Mancuso et al., 2016). Instead, a significant but small effect was seen for working memory training paradigms e.g., where performance on a working memory task was assessed after practicing the same or a different working memory task under stimulation (Mancuso et al., 2016).

Our tongue twister study involved three sessions and as a result it is possible that this resulted in some learning effects which may have interacted with the tDCS stimulation. Therefore, it is possible that, rather than showing evidence for the LIFG role in speech

articulation, our results from anodal stimulation show that the LIFG plays a role in working memory (Fiebach et al., 2005) and that this process can be modulated with LIFG tDCS.

4.4.4 Limitations. There are several methodological limitations to our study. First, as the tongue twister stimuli in our experiment were the same, but randomised, across all sessions, familiarity with the stimuli may have affected performance. It would be possible to control for this familiarity by using three different sets of tongue twisters with similar difficulties for each session in future work.

The flow of current in conventional tDCS is often diffuse because of electrode size, saline spread at the scalp, as well as wide distribution of current flow between the two electrodes (Datta et al., 2011; Lefebvre & Liew, 2017; Nitsche et al., 2007). Therefore, tDCS stimulation may not be focused solely on the region of interest. However, fMRI speech studies have shown that the current is distributed around the targeted region during tDCS (Antal et al., 2012; Holland et al., 2011). Without neuroimaging such as fMRI or neurostimulation (i.e. TMS) to measure cortical excitability, it is not possible to state exactly how much the LIFG was affected by tDCS and how much current spread to other regions. Knowing the spread and effect of the current would allow us greater insight into the mechanism of enhancement observed in our study during tongue twister articulation.

Inter-individual variability is high under tDCS. Some individuals show no effects on corticomotor excitability after tDCS and some individuals even show effects opposite to those predicted (Chew et al., 2015; Nitsche et al., 2004). Varied concentration of GABA observed in the cortex during tDCS stimulation is an indication of inter-individual differences (Kim et al., 2014). This is because improvements in motor learning after anodal tDCS are associated with GABA reductions (Kim et al., 2014). Therefore, an individual's baseline level of GABA is likely to affect the extent of motor learning improvement experienced after anodal tDCS. Individual level of brain-derived neurotrophic factor further seems to influence the response to neurostimulation especially using tDCS (Fritsch et al., 2010; Wang et al., 2011). Research also demonstrates tDCS effects may depend on baseline level of

performance (Hsu et al., 2014). For instance, positive changes can be limited to participants who show poor performance initially (Tseng et al., 2012). Some reports suggest around 40-50% of TS do not show an expected excitatory effect after anodal tDCS or only display minor response to tDCS (Chew et al., 2015; Li et al., 2015; López-Alonso et al., 2014; Strube et al., 2015; Vallence et al., 2015; Wiethoff et al., 2014). In our study, participants showed worsening or small, moderate and large improvements in VRT in response to anodal tDCS illustrating variability of tDCS response.

tDCS may exhibit different effects in different age groups (Perceval et al., 2016), our findings may be limited to relevance within younger populations. Our sample encompassed a narrow age range of participants (19-31). Previous studies which have used tDCS to improve speech processes have largely used samples of older individuals. For example, the mean age of participants in the study by Fiori et al. (2014) was 57 years and, as mentioned, in the study by Holland et al. (2011), mean sample age was 69 years. It may be the case that anodal tDCS induces differential effects in young participants versus older ones. For example, whilst we replicated the findings of Fiori et al. (2014) in a younger sample, the size of the change in response to anodal tDCS was greater in their study. The change in VRT from pre to during stimulation was 1168ms for Fiori et al. (2014) and was 429ms in our study. As these studies aimed to use their findings to inform neurorehabilitation in stroke patients, samples were older. In our study, a younger sample was selected as adults can be affected by stuttering at ages of 18 and above.

4.4.5 Future research. Whilst it has been recognised that effects of tDCS are highly dependent on task-specific neural activity and behavioural demands (Bestmann et al., 2015; Bikson & Rahman, 2013; Pirulli et al., 2014), little research has been conducted examining the effect of behavioural task demands on tDCS performance (Simione et al., 2018). In one study, Simione et al. (2018) demonstrated that anodal tDCS effects on jaw movement depend on task demands as an effect of tDCS was observed for speech and maximum syllable repetition (high demand), but not chewing (low demand).

Further research using conditions of varying complexity, brain imaging and computational models (Datta, Truong, Minhas, Parra & Bikson, 2012) are necessary to elucidate the spread and effect of tDCS current when targeting specific regions engaged in tasks with differential behavioural demands across healthy and impaired populations. Given the complex interaction between polarity and task demands, it is crucial to investigate the specific effects of tDCS on speech motor performance, to optimise the outcomes of tDCS therapeutic trials (Bikson & Rahman, 2013). Such research would then allow for the refinement of neurorehabilitation and intervention protocols based on calculations of maximum tDCS effect on a specific region, function or task.

Such research may also provide insight into alternative regions to target with stimulation. In patient work, the LIFG is targeted as this is often damaged: Stimulating this region leads to improvements in the speech of patients with aphasia (e.g. Marangolo, 2014). In these cases, tDCS appears to induce restorative plasticity by reinstating lost functions (Kleim et al., 2011). Neurorehabilitation frameworks identify other forms of plasticity such as recruiting different brain areas to take over functions performed by damaged areas (Kleim et al., 2011). However, tDCS stimulation procedures that promote other forms of plasticity have not been developed and tested to date (Lu & Howell, 2012). Such procedures might be advantageous in patients where damage to target areas that serve a required function (e.g. LIFG in the case of speech) is extensive.

Future research could also employ alternative tasks to assess speech motor preparation and articulation processes. Such tasks should control for the potential linguistic and semantic influence of stimuli during speech by using non-words and non-lexical items rather than the modulation of consolidated vocabulary as in the present study (Chesters et al., 2017; Westwood et al., 2017). Tasks such as maximum syllable repetition could also be used as they engage the speech motor networks but are likely to only minimally activate linguistic networks that are engaged during meaningful speech (Bohland & Guenther, 2006; Kent, 2015; Ziegler, 2002). Novel Learning paradigms could also provide more positive results, even in control participants (Fiori et al., 2010; Flöel et al., 2008; Meinzer et al.,

2014), because here, as in the case of aphasic patients with brain-damage, representations are weaker and in a more 'plastic' state. Such an approach was employed by Chesters et al. (2017) in their non-word motor learning study.

Finally, although the speech motor performance improvements induced by single tDCS sessions are generally small and relatively short-lived, they accumulate over multiple sessions (Baker et al., 2010; Meinzer et al., 2014; Reis et al., 2009). Repeated tDCS application should allow the positive effects to accumulate and result in significant modulation of functions in healthy and impaired participants (Alonzo et al., 2012; Meinzer et al., 2014). Previous studies have evaluated the potential of multiple sessions of anodal tDCS paired with conventional therapy in facilitating language and speech recovery in individuals with stroke (Fiori et al., 2011; Holland et al., 2011; Holland & Crinion, 2012; Marangolo, 2014; Richardson et al., 2015). However, there have been no multi-session studies in TS to date.

4.4.6 Conclusion. Overall, our findings demonstrate speech articulation processes can be modulated by anodal tDCS over the LIFG during tongue twister repetition. These are most likely to be due an interaction between task complexity and tDCS. In conjunction with our findings from Chapter 3, our studies demonstrate the feasibility of using LIFG tDCS to modulate speech preparation and articulation processes. The results underline the notion that task difficulty is key to induce modulation of function with tDCS. Our results so far show the LIFG can be modulated using tDCS to improve speech production processes. This implies that the LIFG is a valid stimulation target for studies which aim to treat speech disorders. As such, findings can be taken forward to attempt to treat speech disorders such as stuttering, which is characterised by speech preparation and articulation difficulties, using LIFG tDCS.

Chapter 5: Can tDCS improve speech fluency in PWS?

5.1 Introduction

Previous research has suggested that there are structural and functional abnormalities and dysfunction in the LIFG of PWS compared to TS. Consequently, the LIFG appears to have a critical role that leads to stuttered speech in PWS. In Chapters 3 and 4, it was demonstrated that tDCS to the LIFG enhanced TS' speech production skills in both picture naming (two studies) and tongue twister repetition tasks. Given the improvements in fluency in TS when the LIFG is stimulated and the fact that activity in this region is affected in PWS, tDCS was targeted on the LIFG in PWS in the study in this chapter. The hypothesis was that stimulating these dysfunctional regions and networks in PWS should improve their fluency.

5.1.1 Studies using tDCS to treat stuttering. To date, only two studies have explored the use of tDCS as a tool for improving speech production processes in PWS (Chesters, Möttönen & Watkins, 2018; Chesters, Watkins & Möttönen, 2017). These studies used choral speaking and metronome speaking, respectively. Both are interventions where PWS speak in unison with an external trigger (Andrews et al., 1982; Bloodstein & Ratner, 2007; Howell, 2011). Choral speaking involves speaking in unison with another person or recording, whereas metronome speaking involves speaking along with the rhythm of a metronome. As such tasks elicit immediate and effortless fluency in PWS, it has been hypothesised that PWS have a disorder in the generation of internal timing of self-paced speech and/or problems in sensorimotor integration (Alm, 2004; Chang & Zhu, 2013, Etchell et al., 2014, Guitar, 2005, Howell & El-Yaniv, 1987; Max et al., 2004; Packman, Code & Onslow, 2007; Taniwaki et al., 2006; Van Riper, 1982; Watkins et al., 2008; Wu et al., 2011). As a result, when external timing cues are provided, the dysfunctional timing generation can be partially compensated by the external trigger and this leads to a smoother, more fluent, speech movement. This effect is similar to behavioural improvements noted in Parkinson's disease between externally triggered movements compared to self-initiated movements

(Donaldson et al., 2012; Jahanshahi et al., 1995; Lewis et al., 2007; Lim et al., 2005). However, it should be noted that treatment gains do not continue once the stimulus is removed, but nevertheless devices which act as such prostheses are increasingly used by PWS (Howell, 2011). Furthermore, speech quality, particularly with metronome speech, is often rated as having "unnatural" speech timing (Ingham et al., 2012). These same considerations also apply to traditional speech therapy approaches such as fluency-shaping (Howell, 2011). Considerations about speech being unnatural do not apply to Howell, El-Yaniv and Powell's (1987) frequency-shifted feedback, as such an approach induces natural fluent speech. Furthermore, it is possible that the metronome click itself is unique as it can induce fluent speech even when PWS align with self-timed speech rather than externally timed speech (Howell & El-Yanviv, 1987). Whilst treatments based on these procedures may be suitable for some PWS, more conventional forms of treatment also need considering.

In Chesters et al. (2017), 16 PWS received anodal and sham tDCS (1mA for 20 minutes) over the LIFG during two separate sessions (a within subject's design) concurrent with a choral speech tasks. There was a maximum washout period of two weeks between the two sessions. An effect of tDCS (i.e. a reduction in stuttering severity) was not found immediately, or 60 minutes, after the end of stimulation. The authors considered that tDCS effects were absent for several reasons such as because continuous repetition of sentences during the sessions led to adaptation, individual variability with respect to tDCS effects and stuttering severity, the speaking tasks were not challenging, and tDCS was delivered in a single session rather than in multiple sessions.

Chesters et al. (2018) built on their 2017 study and reported a between subjects double blind randomised controlled trial in which 30 PWS received an external trigger intervention alongside tDCS. Stimulation (1mA, 20 minutes) was applied over multiple sessions, one session per day over five consecutive days. Stimulation was targeted over the LIFG and was delivered alongside choral speech and metronome speech tasks. Stuttering severity changes were measured 1 and 6 weeks post-intervention. The intervention increased fluency immediately for participants (including those who received sham

stimulation) but only PWS who received anodal tDCS maintained speech gains at both follow-up test points. Benefits persisted for at least 6 weeks after the intervention ceased and speech naturalness was not affected. However, for the conversation task, at 6 weeks after intervention, dysfluency had returned to baseline although gains were maintained for the reading task. A possible explanation for the persistence of tDCS effects in reading, but not speaking, assessments may be due to a facilitation effect (well-learned or familiar actions are run off fluently; Dockery et al., 2009). Therefore, it is possible that the reading tasks used during choral intervention mirrored the reading outcome measure used post-intervention, but speech did not (Crinion, 2018), leading to longer lasting effects of tDCS.

The Chesters et al. (2018) study was the first multi-session study employing tDCS to address stuttering and provided promising results. Research demonstrated that to make tDCS optimally effective, task-specific neural activation and regions must be targeted with stimulation (Crinion, 2018; Reis & Fritsch, 2011). The ongoing task-based neural activity interacts with the modulatory effect of tDCS, leading to enhanced cortical excitability and neural plasticity (Stagg et al., 2011). The effects of tDCS therefore depend on the level of ongoing activation in the targeted region and associated network (Pisoni et al., 2017; Ruttorf, Kristensen & Schad, 2018) since tDCS current is non-focal and spreads throughout an engaged network. For metronome and choral speaking, engagement of the basal ganglia and cerebellum has been demonstrated to be the central mechanism for fluency enhancement in PWS with these methods (Toyomura et al., 2011; 2015).

5.1.2 Mechanisms of external trigger induced fluency enhancement in PWS.

The mechanisms involved in metronome and choral speech induced fluency enhancement in PWS have been explored by Toyomura et al. (2011). They scanned Japanese PWS and TS with fMRI while they performed metronome, choral and normal speech tasks. Compared to TS, the superior temporal gyrus, IFG, middle frontal gyrus, and basal ganglia (caudate, globus pallidus and putamen) in PWS showed increased activity in choral and metronome conditions compared to normal speaking. TS only showed increased activity in the bilateral

STG and right precuneus. PWS overall showed significantly smaller signal change compared to TS in the normal speaking condition. In a further study, Toyomura et al. (2015) explored the effect of an 8-week metronome intervention on stuttering severity and brain activity in PWS. Pre-intervention scans demonstrated PWS had significantly lower basal ganglia activity, particularly during self-paced speech, compared to TS, replicating their 2011 results. Post-intervention, there was no significant difference in basal ganglia activity between PWS and TS and there was an improvement in speech fluency in PWS. The cerebellar vermis also showed significantly reduced activity post-intervention compared to pre-intervention in PWS. STG activity that was found during metronome and choral speaking in Toyomura et al. (2011) did not change significantly from pre- to post-intervention. The authors suggested that improvement of stuttering with an external cue crucially involves the basal ganglia and cerebellum. This conclusion is consistent with previous research using neuroimaging to assess choral and metronome speaking in PWS (Wu et al., 1995).

Whilst it is not possible to reliably modulate subcortical regions using tDCS, it is likely that the tDCS stimulation-current spreads beyond the targeted region due to the brain being made of highly conductive materials and because it is a non-linear system with multiple interconnected regions and networks (Antal, Polania, Schmidt- Samoa, Dechent, & Paulus, 2011; Engel et al., 2001; Roux & Buzsáki, 2014). For example, stimulation of motor cortex by tDCS can affect supplementary motor area activity and that of linked subcortical regions (Antal et al., 2011; Polanía, Paulus & Nitsche, 2012). However, studies have claimed that around 45% of the tDCS current reaches the cortex (Burger & van Milaan, 1943; Rush & Driscoll, 1968) and declines rapidly with distance from the stimulating electrode (Antal et al., 2012; Holland & Crinion, 2012; Stagg & Johansen-Berg, 2011). Hence, tDCS may have less effect on cortical, and particularly subcortical, structures far from the site of stimulation. As such, rather than tDCS currents directly reaching subcortical regions, they are likely to modulate activity of whole cortico-subcortical networks to produce effects (Peña-Gómez et al., 2012; Woods et al., 2016).

The LIFG is one of several regions, along with the motor, auditory and somatosensory cortices, connected to the basal ganglia within a basal ganglia-thalamo-cortical (BGTC) loop critical for speech motor preparation (Alexander et al., 1986, DeLong et al., 1984). Vanhoutte et al. (2016) found EEG evidence for decreased contingent negative variation (CNV), which is an EEG cortical negative potential, prior to stuttered word production in PWS. CNV activity is thought to reflect motor preparation within the BGTC loop when anticipating producing a response (Bareš et al., 2007; Bender et al., 2004). There was no difference in the CNV of PWS and TS when words were produced fluently. Hence, the reduction in stuttering observed by Chesters et al (2018) is likely to be the result of modulation of the BGTC loop through the LIFG, due to specific basal ganglia involvement in choral and metronome speaking. LIFG tDCS may have resulted in enhanced motor preparation overall, due to the interaction between tDCS and the BGTC network which was engaged during the tasks that involve external cues. Thus, modulation of this BGTC network could reduce stuttering because of its involvement in self-paced movement (Taniwaki et al., 2006; Toyomura et al., 2012), auditory-motor synchronisation (Hove et al., 2013), and observed dysfunction in PWS (Beal et al., 2013; Chang and Zhu, 2013; Lu et al., 2009, 2010). Further tDCS studies employing metronome and choral speech interventions, which also utilise neuroimaging, are required to examine this possibility.

Overall, research demonstrates that speech fluency induced by an external trigger in PWS possibly arises from shifts of activity within basal ganglia, spreading across the speech sensorimotor network, which includes the LIFG. This is consistent with the theory that stuttering results from dysfunction of the basal ganglia in providing timing cues for motor movements (Alm, 2004; Giraud et al., 2008; Lu et al., 2010). However, if the LIFG is directly stimulated, rather than indirectly, speech facilitation may approach optimal levels, and specificity of effects would increase when the intervention used engages the LIFG to reduce stuttering severity. This contrasts with metronome clicks or choral speech that act as a mechanism for fluency enhancement that stimulate intervention mechanisms that indirectly affect the LIFG and the BGTC loops. Fluency shaping methods fulfil the criteria of direct

LIFG involvement in an intervention, which could possibly interact with the tDCS current to produce enhanced modulatory effects (Stagg et al., 2011).

5.1.3 What are fluency-shaping interventions? Fluency-shaping approaches aim to modify speech, reduce dysfluency and lead to natural-sounding spontaneous speech (Blomgren, 2010). Fluency-shaping techniques may include prolonged speech (e.g. prolonging vowels), easy onset (i.e. easing into the first sound of a word), gentle contacts and rate reduction strategies (Van Riper, 1982). With this approach, motor speech muscles are trained in a way that promotes speech fluency (Blomgren, 2013; Montgomery, 2006; Packman, Onslow & Menzies, 2000). Similar to metronome-timed speech, fluency-shaping reduces motor effort, whilst also slowing articulatory movements (Civier, Tasko & Guenther, 2010).

5.1.4 Effectiveness of fluency-shaping interventions. Fluency shaping interventions are the most widely investigated and successful therapy techniques for reducing stuttering severity in PWS (Webster 1977; Blomgren, 2010). Fluency shaping therapies also show the greatest fluency improvements, in both short and long term, and resistance to relapse for severe PWS (Andrews, Guitar & Howie, 1980). Similarly, Euler et al. (2014) assessed the five most common German stuttering treatments (231 single treatment cases). The treatments were rated as to their perceived effectiveness, using a structured questionnaire given to 88 PWS recruited through various sources. Similar findings were also reported by Bothe, Davidow, Bramlett and Ingham (2006), who reviewed the effectiveness of current stuttering treatment approaches.

Fluency-shaping techniques have also been used in standardised therapy approaches. Thus, Franken et al. (1992) conducted a four-week intensive therapy program with 32 severe PWS and compared them with 20 people who did not stutter. They reported that the speech of the PWS improved significantly and the improvement was retained at least over the 6-month follow up period. Fluency shaping approaches have also been used

in therapy programmes such as the Camperdown Program (O'Brian et al., 2003). The Camperdown Program aims to improve or eradicate dysfluency in conversation using prolonged speech (McCauley & Guitar, 2010). The key component to this approach is teaching prolonged speech via imitation of video examples rather than through explicit training of the aspects of prolonged speech (O'Brian et al., 2003). It has been shown that the Camperdown Program facilitates natural-sounding fluent speech within a relatively low number of clinical hours and fluency is maintained for at least 12 months (O'Brian, Onslow, Cream & Packman, 2003).

5.1.5 Neurological effects of fluency-shaping interventions. Fluency-shaping techniques alter the overt speech behaviour of adult PWS and this is accompanied by changes in neurological mechanisms (De Nil et al., 2003). In a treatment outcome study, De Nil et al. (2003) tested the short-term and long-term effects of a modified version of the Precision Fluency Shaping Program (Webster, 1974), that incorporates fluency shaping techniques, on stuttering severity. Position Emission Tomography (PET) imaging was used to examine neural activity after three weeks of intensive treatment and one year following a maintenance program. Participants presented with significant reductions in stuttering severity. This was accompanied by reduced over-activation in the motor cortex and a shift in lateralisation to the left hemisphere, particularly from bilateral to left hemisphere activation in the LIFG post-therapy. Moreover, in De Nil et al (2003), at the one-year follow-up participants not only showed increased dysfluency but also some re-lateralisation to the right hemisphere. However, this study involved a single word reading task, which raises some questions about whether fluency would transfer to spontaneous conversational speech (Cordes, 1998).

Similar results were also observed by Neumann et al. (2005), where a leftward shift of neural activity was observed post fluency-shaping intervention, from overactive right hemisphere regions such as the RIFG to normalised activity (i.e. comparable to TS) in the LIFG and left STG. One year after treatment, this activity in the LIFG and left STG

increased, and more distributed neural activation occurred bilaterally in the premotor and motor cortex. Some right-dominant lateralisation re-emerged two years post-treatment with an increase in stuttering behaviour. Fluency shaping methods emphasise constant on-going self- monitoring of speech that require focused attention, and slow articulatory movements. Hence, it is hypothesised that fluency-shaping increases speech motor control and reduces motor effort in PWS by reorganising neuronal communication between left sided speech motor planning, motor execution areas (De Nil et al., 2003; Neumann et al., 2005; Packman, Code & Onslow, 2007). Hence, as a result of applying tDCS to the LIFG, the current is likely to directly affect the LIFG, enhancing speech motor plan formulation through increased cortical excitability and efficiency of task-related LIFG processes. This current is also likely to enhance the communication of these speech motor plans to LIFG interconnected regions, through spreading activation, such as the orofacial motor cortex (Neef et al., 2015; Salmelin et al., 2000), thereby facilitating fluent speech further.

The mechanisms behind fluency improvement in PWS using fluency shaping methods and speaking with an external trigger therefore overlap. Both methods can induce bilateral/leftward shifts in neural activation in cortical and subcortical speech motor regions such as the IFG and the basal ganglia. Speaking with an external trigger theoretically compensates for impaired internal rhythm generation and sensorimotor integration in the basal ganglia of PWS (Neumann et al., 2005). Fluency shaping probably improves speech motor production by allowing the speaker to focus attention on fluent speech planning and production, subsequently utilising and engaging more left lateralised speech areas such as the LIFG to enable efficient speech motor planning.

However, a key difference between fluency-shaping and external trigger interventions is the ease of acquisition of fluent speech between the interventions. Metronome and choral speech induce fluent and effortless speech instantly (Andrews et al., 1982; Bloodstein and Ratner, 2007). This contrasts with fluency shaping therapies that require practice, effort and monitoring (Blomgren, 2010). The level of effort and demand required in a task interacts with the effect of tDCS (Hsu, Juan & Tseng, 2016), particularly

for demands on jaw movement (Simione et al., 2018). Task difficulty and challenge therefore further affect the level of positive effects induced by tDCS. Difficult and challenging tasks are thought to result in increased engagement of targeted regions, leading to greater specificity of stimulation effects demonstrated in Chapter 4 and in previous research (Crinion, 2018; Fiori et al., 2014). Fluency shaping is therefore a method which, when applied alongside tDCS, would result in normalised (compared to TS) engagement of the LIFG. This engagement could then interact with the tDCS current to modulate cortical excitability and synaptic plasticity to enable enhanced LIFG functioning and consequently, enhanced speech planning resulting in a reduction in stuttering.

5.1.6 Involvement of plasticity mechanisms in intervention. The LIFG is often targeted in speech rehabilitation intervention work as this is often damaged in aphasic patients. Stimulating this region leads to improvements in the speech of patients with aphasia (de Aguiar et al., 2015; Fiori et al., 2011; Fridriksson et al., 2011; Holland et al., 2011; Holland & Crinion, 2012; Marangolo, 2014; Richardson et al., 2014). One way in which tDCS can help patients with aphasia is through restorative plasticity. In these cases, tCDS is thought to reduce synaptic membrane potential, reducing the level of excitatory input required to engage a region and thus increasing cortical excitability. Consequently, increased cortical excitability allows for more significant involvement of impaired regions, in tasks which engage the impaired region. As a result, tDCS can help to reinstate lost functions through increased engagement of an impaired region within relevant tasks (Kleim et al., 2011). A further method by which tDCS is thought to help patients with aphasia is through retraining plasticity, whereby through retraining via challenging interventions and tasks, functional reorganisation of plasticity is driven through long-tern potentiation and long-term depression mechanisms which are modulated by tDCS (Kleim et al., 2011). Neurorehabilitation frameworks identify other forms of plasticity such as recruiting different brain areas to take over functions performed by damaged areas (Kleim et al., 2011).

However, tDCS stimulation procedures that promote other forms of plasticity have not been developed and tested to date (Lu & Howell, 2012).

Plasticity induction is an essential part of positive therapy outcomes, hence the use of a protocol that employs and engages plasticity principles and mechanisms is essential. Furthermore, as tDCS does not facilitate behavioural changes on its own, but rather maximises the effectiveness of challenging behavioural techniques, selecting an effective but challenging behavioural intervention is critical (Holland & Crinion, 2012). Therefore, the present study investigated whether a challenging fluency-shaping intervention that engages speech motor circuits, exploits plasticity principles and incorporates concurrent brain stimulation leads to a reduction of stuttering severity in PWS.

5.1.7 Current study. The study investigated whether applying anodal tDCS to the LIFG concurrently with fluency-shaping therapy reduced stuttering severity in PWS more than sham tDCS did. Stimulation, combined with therapy, was delivered over 5 sessions. This study was based on research that demonstrates positive tDCS effects are more likely to be obtained with multiple sessions of tDCS in both TS (Dockery et al., 2009; Flöel et al., 2008; Kadosh et al., 2010; Meinzer et al., 2013, 2014; Reis et al., 2009) and brain-damaged populations (Baker et al., 2010; Fiori et al., 2011, 2013; Fridriksson et al., 2011; Marangolo et al., 2011, 2013).

Fluency-shaping techniques were chosen due to the strong evidence-base in terms of: (1) reducing stuttering severity (Andrews et al., 1980; Blomgren, 2010); (2) the therapy results in leftward shifts of neural activity that is similar to the typical pattern observed in TS (De Nil et al., 2003; Neumann et al., 2005); (3) decreased LIFG activity is directly linked to increased stuttering severity (Neef et al., 2016); and (4) research has demonstrated that increasing functional activity within the LIFG is a key component in recovery from stuttering (Kell et al., 2009; 2018).

PWS received anodal tDCS, or Sham tDCS, to the LIFG along with fluency-shaping therapy. To assess stuttering severity, the Stuttering Severity Instrument (SSI-3; Riley, 1994)

was used. The SSI-3 is a widely used, reliable screening tool for stuttering (Howell, 2013; Riley, 1994). In addition to the SSI-3, the percentage syllables stuttered were also calculated for speaking and reading to assess stuttering severity. It was hypothesised that the Anodal tDCS group would show a significantly greater reduction in stuttering severity between pre and post-intervention time points on SSI-3 scores, percentage syllables stuttered during speaking and percentage syllables stuttered during reading. It was considered that these effects could be achieved through facilitation of brain circuits that support fluent speech and promote neural plasticity, for example, through improved communication between the LIFG and speech motor cortex.

5.2 Method

5.2.1 Participants. There were 14 participants in total (11 male) split across anodal tDCS (N = 7, M= 27.57, SD = 9.41, Range= 20-45 years) and sham tDCS (N = 7, M= 28.57, SD = 10.06, Range= 20-46) groups. The average score on the SSI-3 across participants for the anodal group was 25.86 (SD= 7.81). For the sham group, the average SSI-3 score was 24.71 (SD= 12.56). Group averages were moderate and mild respectively.

Participants were fluent right-handed, English speakers aged between 18 and 65 years of age. They had been diagnosed by a Speech and Language Therapist (SLT) as stuttering (this varied from very mild to very severe). They gave informed consent and committed to attend for all five sessions. PWS not meeting any of these criteria were excluded from the study. Due to the use of electrical stimulation and to minimise extraneous variables, participants were also excluded if they presented with an additional speech, language or communication disorder; history of a major physical disease; neurosurgery that included use of metallic clips; drug abuse or neurological disease, for instance head trauma, epilepsy, psychiatric illness; or participants who were currently receiving other forms of speech and language therapy.

Convenience sampling was used as participants were required to come into the university campus for each therapy session. Participants were recruited by various means which included: adverts on social media, contact with support group and stuttering charities, and information letters sent to a number of SLT Managers working in NHS health trusts in North West and Central London.

5.2.2 Design. The design was a 2x2 double blind mixed intervention study that compared pre- and post-treatment changes following the use of anodal tDCS or sham tDCS in conjunction with fluency-shaping therapy. The first (between-subjects) factor was the stimulation condition (anodal tDCS or sham tDCS), which were the independent variables, both of which were combined with fluency-shaping therapy. The second (within-subjects) factors, the dependent variables, were the percentage change in syllables stuttered across

speaking and reading tasks and SSI-3 scores pre and post-intervention. The experimental condition involved delivery of anodal tDCS alongside fluency-shaping therapy; the control condition involved sham tDCS alongside fluency-shaping therapy. A total of five sessions were delivered over a 14-day period. Participants and researchers were unaware of which condition participants had been assigned to during the treatment phase. One or two qualified SLTs conducted all treatment sessions.

5.2.3 Materials. A screening test was completed online that ensured that participants met the inclusion criteria. This screening included questions regarding the inclusion criteria e.g. history of neurological disease and screening of handedness via the Edinburgh Handedness Inventory (Oldfield, 1971).

The SSI-3 was used in this experiment to assess stuttering severity pre and post intervention. This measure requires recordings of a short conversation and reading a standard passage. The order of the conversation and reading assessments was counterbalanced across participants. The conversation and reading speech samples were analysed and rated on three components: percentage of syllables stuttered (%SS), duration of stuttering events and physical concomitants (distracting sounds, facial grimaces, head movements and movements of the extremities). The SSI-3 was used instead of the SSI-4 as the additional features of the SSI-4 have not been tested for reliability or validity and additional tests in SSI-4 are not necessary for the severity assessment of the stutter (Howell 2013). According to the recommendations of the test, a minimum of 200 syllables must be analysed to produce a reliable stuttering severity measure. This recommendation was supported by a study that evaluated the SSI-3 reliability (Todd et al., 2014).

5.2.4 tDCS. The tDCS stimulation protocol used in this study was identical to the protocol used in Chapters 3 and 4. In summary, 2 mA (36 seconds ramp up) of tDCS was applied over the LIFG (F5 on the EEG 10-20 system) with the reference electrode placed over the contralateral supraorbital ridge. This set up was used in both anodal and sham

tDCS conditions. The tDCS stimulation was applied for 20 minutes. At the end of stimulation, the therapy session continued for around 30-40 minutes, as research has shown that the positive after effects of tDCS can last for up to 1 hour (Nitsche & Paulus, 2001).

Online anodal tDCS (2 mA) was chosen because of the positive effects of this protocol on speech production in TS in Chapters 3 and 4. In addition, online tDCS was chosen due to the effectiveness of online LIFG stimulation protocols in the treatment of speech impairments in patients with aphasia (Baker et al., 2010; Fridriksson et al., 2011; Vestito et al., 2014). Research further suggests of 2 mA tDCS results in better responses at the group level compared to 1mA or 0.5 mA (Chew et al., 2015). In addition, according to Ammann, Lindquist and Celnik (2017), multiple sessions of 2mA tDCS reduces stimulation variability at the group level when compared to 1mA current. In their study, they observed 2 mA anodal tDCS resulted in consistent intra- and inter-individual increases of cortical excitability compared to 1 mA.

5.2.5 Therapy and procedure. Therapy was delivered by qualified SLTs who were trained in use the of tDCS equipment and this was done under NB's supervision (he attended and supervised throughout).

The five sessions of therapy were delivered over a fourteen-day period with a gap of at least 24 hours between each stimulation session. Each therapy session lasted between 45 and 60 minutes including the set-up of equipment. Participants were taught the use of two fluency-shaping techniques during sessions: prolongation and easy onset. Electrodes for tDCS were positioned on the heads of participants throughout the session regardless of whether they received anodal or sham tDCS. Pre- and post-assessment tasks were completed in the absence of stimulation. The pre-intervention SSI-3 was completed immediately once participants arrived at the testing room prior to the first session. The post intervention SSI-3 assessment was completed immediately following the end of the intervention session. Verbal records of assessments were recorded using Audacity software

and a Yeti USB microphone that was placed 10 cm away from participants' mouths, approximately 20 degrees from upright.

In the first three sessions, participants practiced prolongation and easy onset techniques separately on monosyllabic, disyllabic, trisyllabic and higher order multisyllabic words, short phrases and long sentences and conversation under SLTs guidance. Participants were instructed to elongate vowels rather than initial sounds during prolongation, to avoid reinforcement of dysfluency (Hegde, 2007). Techniques were modelled for the participants for each stimulus item and feedback was given immediately following the participant's attempts. Objectives revolved around articulation, speech rate, breathing and loudness. As sessions progressed, difficulty increased from using the techniques at a CV level (e.g. ho, ha, to) to a pressured conversation (e.g. asking the PWS about certain topics and then interrupting them and simulating high anxiety conversations). The rate at which participants progressed through these stimuli depended on their acquisition of, and success with, each technique. The last two sessions were focused mainly on monologue and conversations with the participants using both techniques in their speech. During the final session, participants were asked to give a ten-minute verbal presentation on a topic of their choice. The aim of this activity was to facilitate integration of prolongation and easy onset techniques under situations that increased pressure to establish whether it promoted generalisation and maintenance.

5.2.6 Analysis. A speech sample for SSI-3 analysis was recorded during conversation and reading. All recordings were transcribed aiming for a 200-syllable sample of speaking for each participant in the speaking task. The recordings were transcribed by the SLTs and the percentage of stuttered syllables was calculated. Stuttered syllables were denoted as repetitions and prolongations of phonemes or syllables, hesitations and blocks. Interjections, repetitive multisyllabic words or phrases were not counted. Inter-rater reliability was assessed between the two SLT's revealing a high percentage of agreement between scores (91.4% pre-intervention and 94.3% post-intervention).

Three mixed ANOVA's were performed with tDCS stimulation (Anodal or Sham) as a between groups factor, and pre and post intervention scores (time; within subject's factor) for dependent variables speaking (% syllables stuttered), reading (% syllables stuttered) and SSI-3 assessments. All significant results were followed up with independent samples t-tests. Descriptive and inferential statistics were calculated using SPSS (v. 22, IBM).

5.3 Results

Stuttering severity varied considerably across participants in our sample, ranging from 1% to 19.4% %SS in the speaking assessment and 1.25% to 35.60% in the reading assessment. Consequently, SSI-3 scores within our sample ranged from 10 (very mild, 1-4 percentile) to 48 (very severe, 99th percentile). The PWS with the extreme SSI-3 score of 48, referred to from here onwards as Participant 14 (P14), was a statistical outlier at the pre-intervention speaking baseline task (>2SD away from the group mean) and at the pre-intervention reading baseline task (>3SD away from the group mean). The post-intervention scores for this participant were also outliers (>2SD) for both post-intervention speech and reading tasks. For completeness and rigor, results of analysis are reported with this participant both included and excluded from analysis.

5.3.1 SSI-3 Scores. ANOVA's (Table 15) revealed main effects of time, p = .001 and p = .003, with P14 included and excluded respectively. This indicated that total SSI-3 scores significantly reduced from pre to post intervention time points when P14 was both included (pre mean: 23.28, SE: 2.797; post mean: 18.42, SE: 2.453) and excluded (pre mean: 23.34, SE: 2.190; post mean: 16.76, SE: 1.957) from analysis. However, no significant interactions were observed. Subsequent independent samples t-tests were used to explore mean differences. As shown in Tables 16 and 17, there was no significant difference in SSI-3 scores between the Anodal and Sham tDCS groups at pre or post intervention with P14 included (Figure 13) and excluded (Figure 14). The percentage change from pre-stimulation, although larger in Anodal compared to sham in both analyses, was also not significant.

Table 15.

Results of ANOVAs for SSI-3 scores with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	F-value	p-value	df	F-value	p-value	df
Time	**18.142**	**0.001**	**12**	**14.571**	**0.003**	**11**
Time * tDCS Stimulation	1.772	0.208	12	1.963	0.189	11

Table 16.

Results of Independent Samples t-tests for SSI-3 scores across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	T-value	*p-value*	*df*	*T-value*	*p-value*	*df*
Pre	-0.204	0.842	12	-1.147	0.276	11
Post	-0.641	0.534	12	-0.065	0.949	11
% Change	1.279	0.244	12	-1.137	0.28	11

Table 17.

Mean (SD) SSI-3 scores across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included		P14 Excluded	
	Anodal	*Sham*	*Anodal*	*Sham*
Pre	25.85 (7.81)	24.71 (12.56)	25.85 (7.81)	20.83 (7.93)
Post	16.85 (7.49)	20 (10.59)	16.85 (7.49)	16.66 (6.43)
% Change	32.21 (26.06)	19.30 (5.85)	32.21 (26.06)	19.74 (6.28)

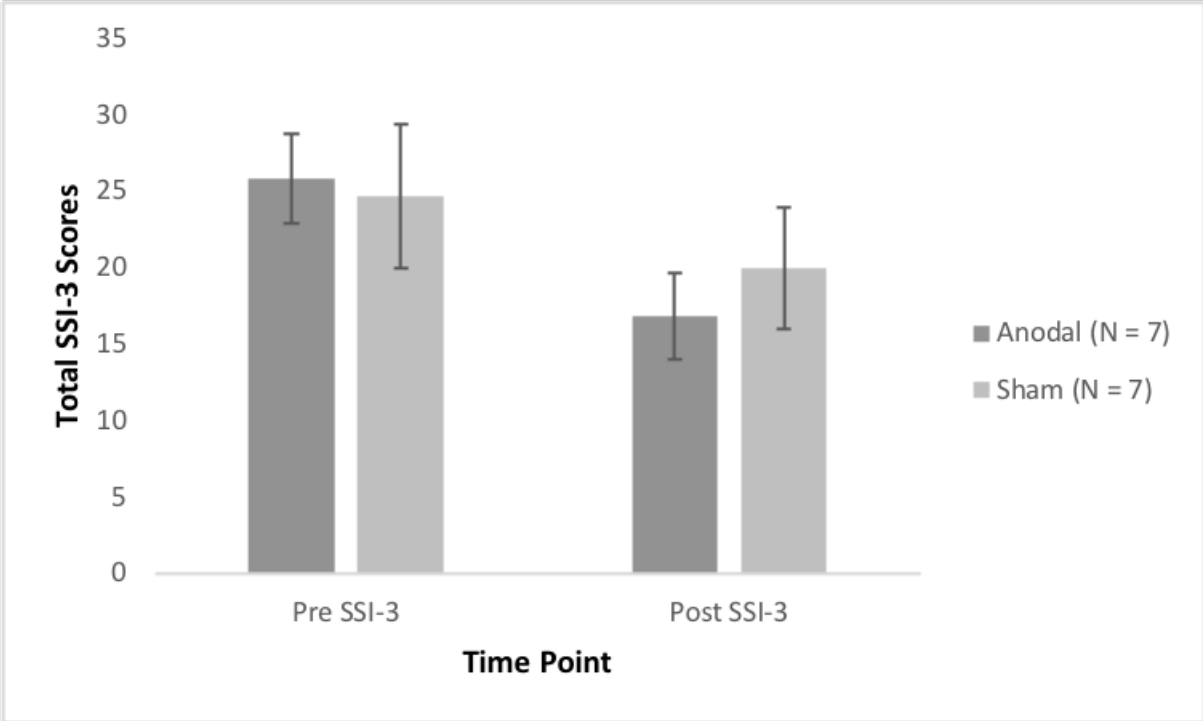

Figure 13. Total SSI-3 scores (high scores indicate greater stuttering severity) for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 is included in the data in this graph. Error bars represent +/ one standard error of the mean.

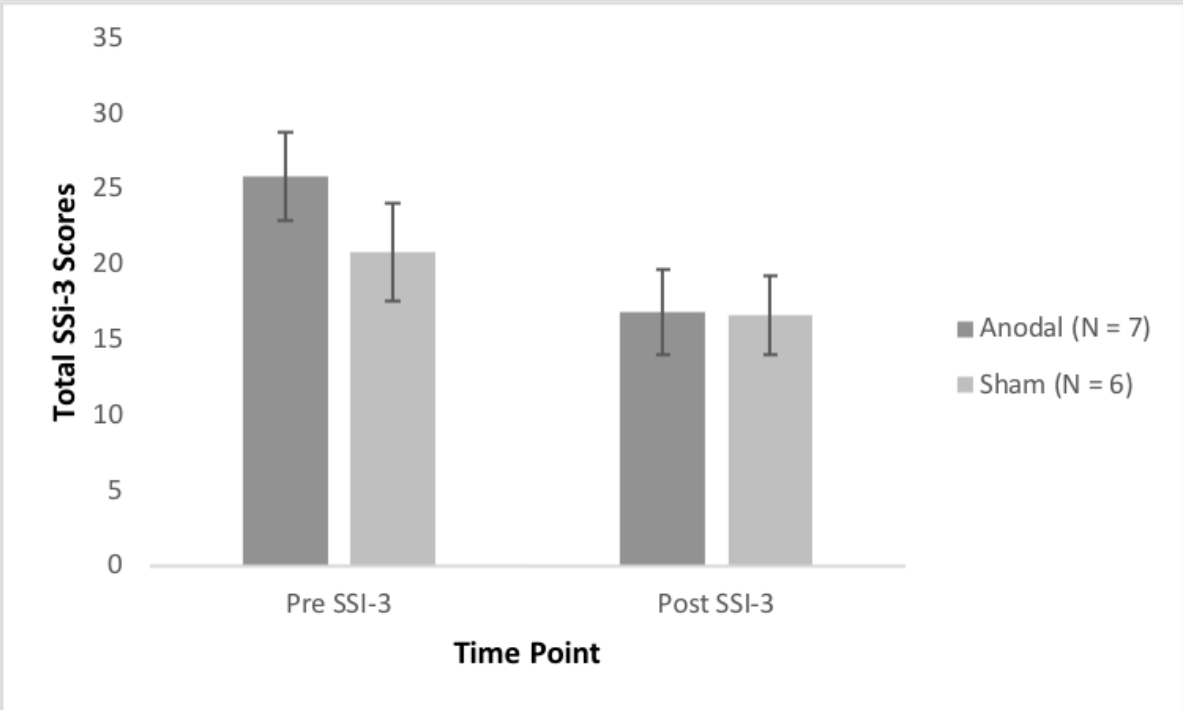

Figure 14. Total SSI-3 scores (high scores indicate greater stuttering severity) for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 was excluded from the data in this graph. Error bars represent +/ one standard error of the mean.

5.3.2 Percentage stuttered syllables – speaking. ANOVA's (Table 18) revealed main effects of time, p = .001 and p = .002, with P14 included and excluded respectively. This indicated that the percentage of stuttered syllables during the speaking task significantly reduced from pre to post intervention time points when P14 was both included (pre mean: 7.614, SE: 1.259; post mean: 5.171, SE: 1.099) and excluded (pre mean: 6.667, SE: .901; post mean: 4.364, SE: .811) from analysis. Interactions were found to be trending towards significance when P14 was included and stronger when P14 was excluded. These trending interactions indicate that the percentage syllables stuttered reduction during speaking, between pre and post intervention, was affected differently by anodal and sham tDCS in PWS. Subsequent independent samples t-tests were used to explore mean differences. As shown in Tables 19 and 20, there was no significant difference in percentage syllables stuttered between the Anodal and Sham tDCS groups at pre or post intervention with P14 included (Figure 15) and excluded (Figure 16). However, the percentage change of

syllables stuttered during speaking was greater from pre-stimulation to post stimulation for the Anodal group compared to Sham. This difference was trending towards significance with P14 included (p = .084), and this trend became stronger when P14 was excluded (p = .062). Again, these trending interactions suggest the percentage syllables stuttered reduction during speaking, between pre and post intervention, was affected differently by anodal and sham tDCS in PWS.

Table 18.

Results of ANOVAs for percentage syllables stuttered during speaking with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	F-value	*p-value*	*df*	*F-value*	*p-value*	*df*
Time	**20.01**	**0.001**	**12**	**16.099**	**0.002**	**11**
Time * tDCS Stimulation	**3.546**	**0.084**	**12**	**4.151**	**0.066**	**11**

Table 19.

Results of Independent Samples t-tests for percentage syllables stuttered differences during speaking across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	T-value	*p-value*	*df*	*T-value*	*p-value*	*df*
Pre	-0.329	0.748	12	0.592	0.566	11
Post	-1.313	0.214	12	-0.781	0.452	11
% Change	**1.883**	**0.084**	**12**	**2.162**	**0.062**	**11**

Table 20.

Mean (SD) percentage syllables stuttered during speaking across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included		P14 Excluded	
	Anodal	*Sham*	*Anodal*	*Sham*
Pre	7.2 (2.92)	8 (5.98)	7.2 (2.92)	6.13 (3.57)
Post	3.72 (2.84)	6.61 (5.07)	3.72 (2.84)	5 (2.99)
% Change	3.47 (2.61)	1.41 (1.23)	3.47 (2.61)	1.13 (1.08)

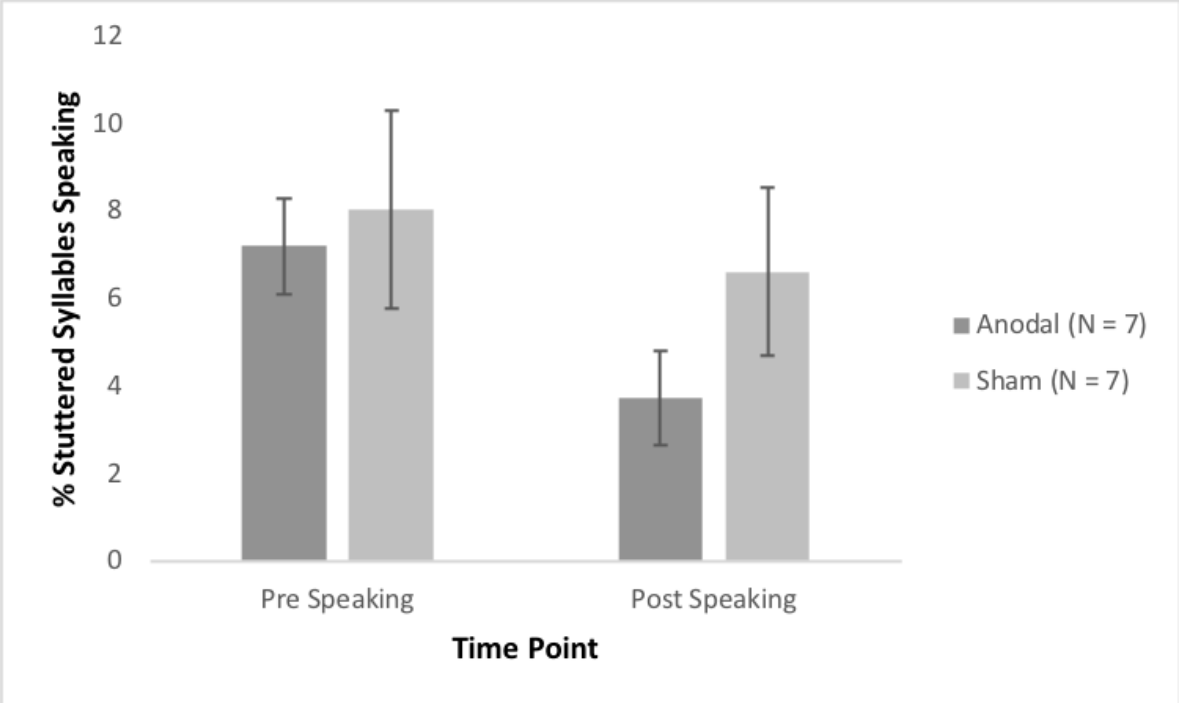

Figure 15. Percentage stuttered syllables scores during the speaking assessment for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 is included in the data in this graph. Error bars represent +/ one standard error of the mean.

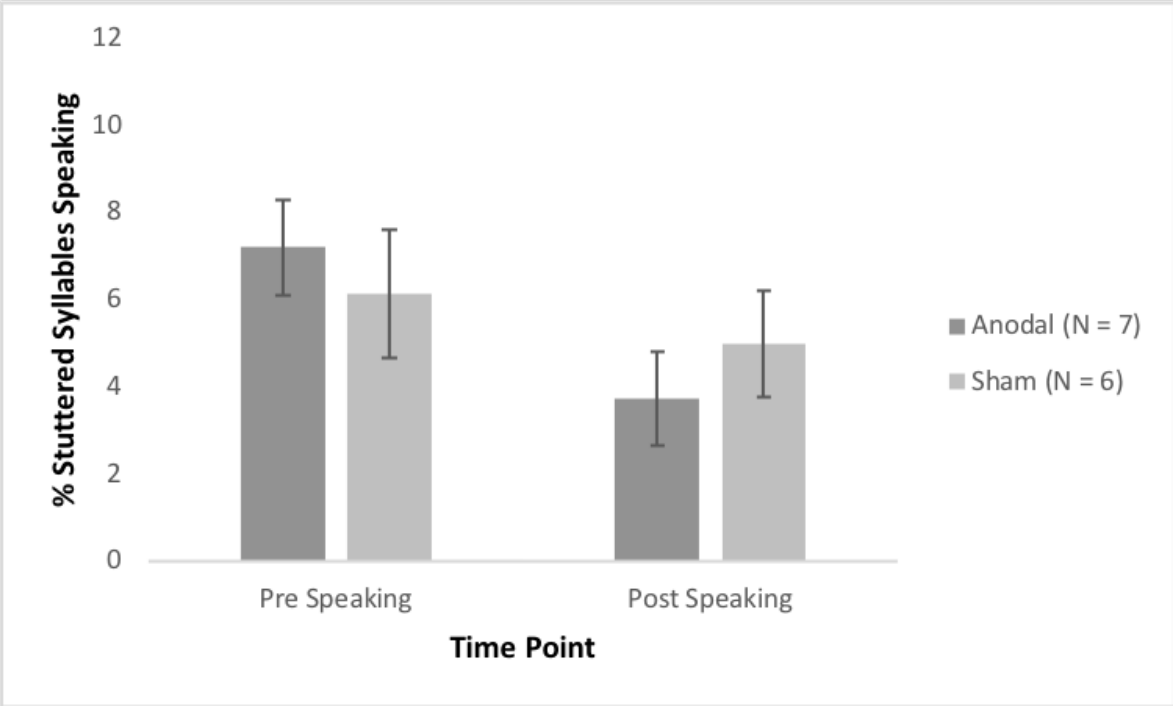

Figure 16. Percentage stuttered syllables scores during the speaking assessment for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 was excluded from the data in this graph. Error bars represent +/ one standard error of the mean.

5.3.3 Percentage stuttered syllables – reading. ANOVA's (Table 21) revealed main effects of time, p = .014 and p = .001, with P14 included and excluded respectively. This indicated that the percentage of stuttered syllables during the reading task significantly reduced from pre to post intervention time points when P14 was both included (pre mean: 8.412, SE: 2.517; post mean: 3.532, SE: 1.178) and excluded (pre mean: 6.158, SE: 1.215; post mean: 2.837, SE: 1.034) from analysis.

A significant interaction (p = .019) was also observed between time and tDCS stimulation when P14 was excluded. This indicated that the percentage syllables stuttered reduction during reading, between pre and post intervention, was affected differently by anodal and sham tDCS in PWS. Subsequent independent samples t-tests were used to explore mean differences. As shown in Tables 22 and 23, there were no significant difference in percentage syllables stuttered during reading between the Anodal and Sham tDCS groups at pre or post intervention with P14 included (Figure 17) and excluded (Figure

18). The percentage change of syllables stuttered when reading from pre to post intervention was also not significant. Means however showed that with P14 excluded, the Anodal group had a 2.61% greater decrease in syllables stuttered during reading compared to Sham.

Table 21.

Results of ANOVAs for percentage syllables stuttered during reading with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	F-value	*p-value*	*df*	*F-value*	*p-value*	*df*
Time	**8.187**	**0.014**	**12**	**19.585**	**0.001**	**11**
Time * tDCS Stimulation	0.084	0.776	12	**7.505**	**0.019**	**11**

Table 22.

Results of Independent Samples t-tests for percentage syllables stuttered during reading differences across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included			P14 Excluded		
	T-value	*p-value*	*df*	*T-value*	*p-value*	*df*
Pre	-0.053	0.959	12	-1.747	0.109	11
Post	-0.533	0.604	12	0.065	0.949	11
% Change	-0.088	0.932	12	1.453	0.181	11

Table 23.

Mean (SD) percentage syllables stuttered during reading across time points between Anodal and Sham tDCS groups with P14 included and excluded from analysis

	P14 Included		P14 Excluded	
	Anodal	*Sham*	*Anodal*	*Sham*
Pre	8.28 (5.37)	8.54 (12.18)	8.28 (5.37)	4.03 (2.70)
Post	2.90 (4.01)	4.16 (4.77)	2.90 (4.01)	2.77 (3.32)
% Change	5.37 (3.52)	5.67 (8.15)	5.37 (3.52)	2.76 (2.98)

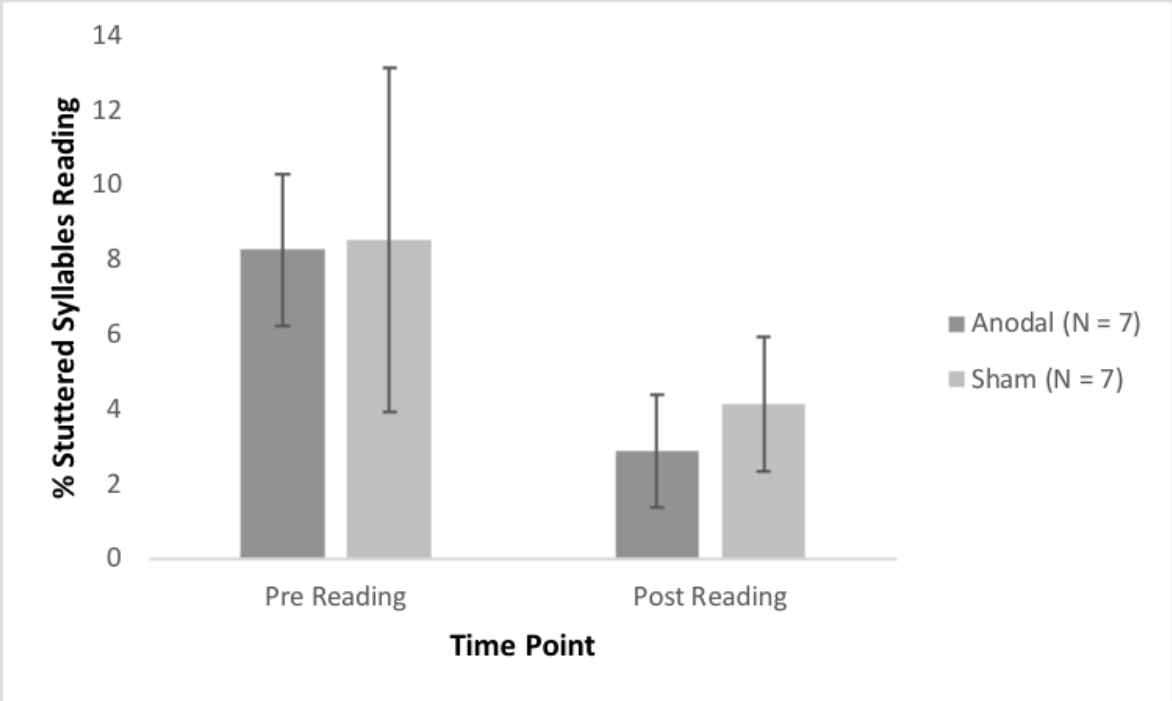

Figure 17. Percentage stuttered syllables scores during the reading assessment for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 is included in the data in this graph. Error bars represent +/ one standard error of the mean.

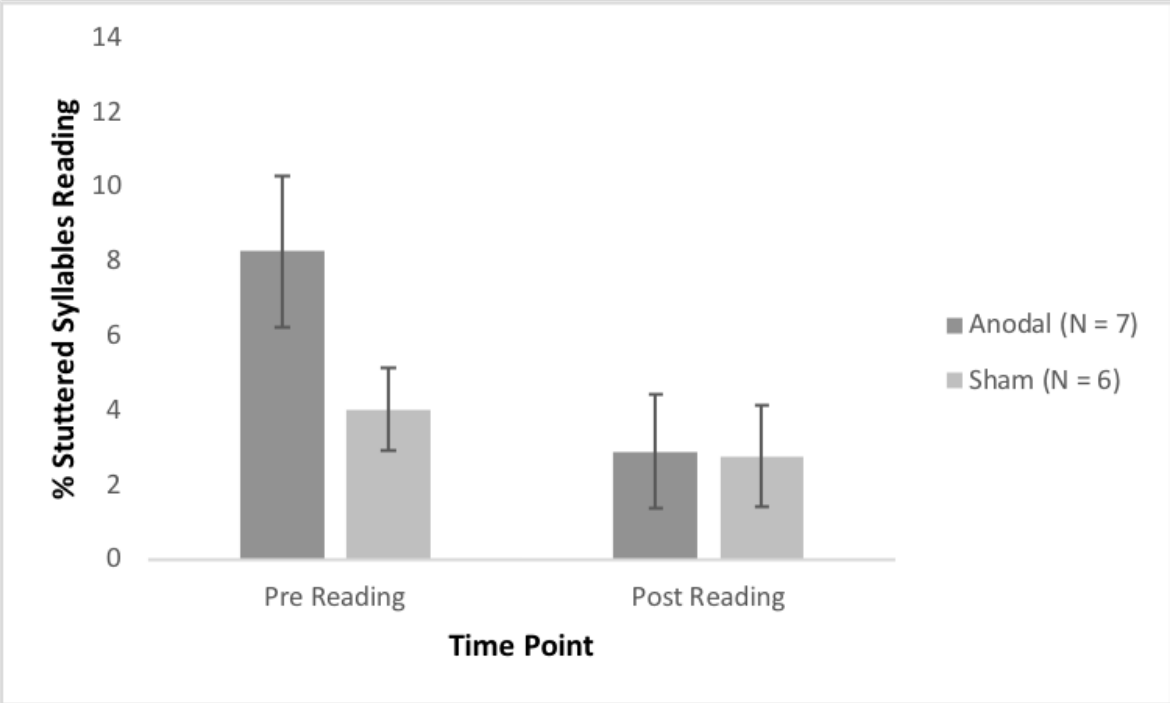

Figure 18. Percentage stuttered syllables scores during the reading assessment for Anodal and Sham tDCS groups across pre and post-intervention time points. P14 is not included in the data in this graph. Error bars represent +/ one standard error of the mean.

5.3.4 Summary. Overall results demonstrated that the group of PWS who received anodal tDCS displayed greater change in stuttering severity from pre to post-assessment across SSI-3 scores and percentage syllables stuttered during speaking and reading tasks. Although the majority of these differences were not significant, differences in the percentage syllables stuttered in the speaking assessment were trending towards significance with and without the inclusion of outlier P14. When P14 was excluded, the ANOVA showed a significant interaction between time point and tDCS condition. Inspection of means revealed the anodal group displayed a greater percentage of syllables stuttered during the pre-time point compared to sham, and no difference between anodal and sham group at the post-time point, possibly indicating a floor-effect.

5.4 Discussion

Anodal tDCS or sham tDCS was applied to the LIFG of PWS, alongside fluency shaping therapy and any effect of tDCS on reducing stuttering was measured. The results showed that PWS who received anodal tDCS displayed greater change in stuttering severity from pre to post-assessment across SSI-3 scores and percentage syllables stuttered during speaking and reading tasks. These differences between pre and post-intervention time points were not significant for SSI-3 scores and percentage syllables stuttered during the reading task but were trending towards significance for percentage syllables stuttered during the speaking task. As stuttering reductions were observed between the anodal and sham groups, but were not significant, our hypothesis was only partially supported. These findings are promising, particularly as the speaking assessment involved conversation, which provides an ecologically valid indication of stuttering severity. Overall, the results suggest anodal tDCS over the LIFG can potentially lead to a greater reduction in stuttering severity during conversation when applied alongside fluency shaping therapy methods with PWS.

5.4.1 Findings. The findings show that applying tDCS over the LIFG can potentially be beneficial for the purposes of reducing stuttering severity in PWS and improving speech production processes. Furthermore, this is consistent with previous research on TS (e.g. Fiori et al., 2014) and our findings in Chapters 3 and 4 also involving TS; as well as aphasia studies showing speech improvement after LIFG tDCS (e.g. Marangolo et al., 2013). Research showing the LIFG is a crucial region involved in stuttering and recovery (e.g. Neef et al., 2016); and (3) tDCS intervention studies with PWS which applied tDCS over the LIFG alongside an intervention (Chesters et al., 2017; 2018) to reduce stuttering. The improvement in stuttering severity, albeit marginally significant, observed in our study and by Chesters et al. (2017; 2018) after LIFG tDCS possibly results from the action of two mechanisms. First, increases in LIFG excitability may lead to increased efficiency of speech planning processes (Long et al., 2016). Second, LIFG tDCS probably results in improved coordination between the LIFG and regions/networks which enable fluent speech production

such as the orofacial motor cortex (Neef et al., 2015). However, as neuroimaging was not used to assess tDCS effects in either study, these ideas must to verified in future work.

The percentage changes between pre and post-intervention in our study during the conversation assessment were comparable to those reported by Chesters et al. (2018) in their tDCS intervention study with PWS. Chesters et al. (2018) found a 3.24% reduction in stuttered syllables during conversation post-intervention compared to baseline, whereas the sham group showed a 0.51% reduction in stuttering post intervention. For comparison, we observed a 3.47% reduction in stuttered speaking syllables post-intervention in the anodal tDCS group and a 1.41%/1.13% reduction in the Sham tDCS group (with P14 included and excluded respectively). Use of a fluency shaping intervention alongside LIFG tDCS therefore seems to produce similar reductions in percentage stuttered syllables compared to a metronome based tDCS intervention in PWS. However, as our effects are currently trends rather than significance, further research is warranted to validate the efficacy of our fluency shaping intervention.

5.4.2 Explanations of our results.

5.4.2.1 Small sample size. The immediate explanation for our trends towards, rather than strong, significance is the small sample of this pilot study (n = 14). Small sample sizes lead to low power to detect significant differences, potential issues with type I errors and low reproducibility (Lefaucheur et al., 2017). Whilst a power analysis was not possible due to the lack of previous similar studies to estimate expected effects, the typical power achieved across cognitive tDCS studies recruiting 20 to 30 participants is roughly 14% (Medina & Cason, 2017). Low power naturally reduces the probability of finding a significant effect if one in fact truly exists, but it also gives undue weight effects which could be significant by chance (Button et al., 2013; Minarik et al., 2016).

Previous between group tDCS intervention studies in patients with aphasia have shown medium effect sizes with samples of 10 participants per group in a between subject's

design (Baker et al., 2010). A within subject's design may not be the ideal design for intervention studies involving PWS due to the potentially high variability of stuttering at baseline across PWS (Chesters et al., 2017). Consequently, samples of around 15 per group for PWS in a between subject's design have been suggested to be required to elicit 80% power to detect a large effect size (Chesters et al., 2018).

Recent research has provided further guidelines about the number of participants required for reliable analysis and study quality in tDCS studies. A recent review by Lefaucheur et al. (2017) provided criteria to classify the quality of tDCS studies based on guidelines by the European Federation of Neurological Societies (Brainin et al., 2004). Class I studies require more than 25 participants per group to detect differences in a between group study design. Class II studies require a sample of 10-24 participants per group, in addition to a sham tDCS control group. Class III studies consist of less than 10 patients, whereas Class IV studies are uncontrolled, case series or case reports. Hence, with 7 participants per group our current tDCS study with PWS falls into a Class III and is likely to be underpowered. At least three more participants are required per group to bring the total up to 10 per group to qualify as a Class II study and improve overall reliability and statistical power.

5.4.2.2 High variability of stuttering across PWS. A potential explanation for the trends in our study, and an issue to be addressed to improve effects, is the wide variability of stuttering across participants. PWS in our study ranged in severity, as assessed by the SSI-3, from very mild to very severe. For example, the percentage of syllables stuttered during reading assessment at pre-intervention varied between anodal and sham groups was similar (8.28% Anodal and 8.54% Sham) when outlier P14 was included, but the mean percentage of stuttered syllables was 4.25% (anodal: 8.28%, sham: 4.03%) greater in the anodal condition compared to sham when P14 was excluded. Hence, the variability of stuttering across our sample potentially contributed to lack of effects or trends observed in the reading assessment. A homogenous sample of PWS with similar severity levels is desirable in future

tDCS intervention studies with PWS to detect effects under conditions of improved sensitivity.

Alongside these variations in severity are structural and functional variations across individuals, and possible variations in the neurophysiological underpinning of stuttering for each individual. One fMRI study on stuttering showed that no common cortical region was active in speech tasks across four PWS although the activation patterns were consistent over time within a given individual (Wymbs et al., 2013). Furthermore, Ingham et al. (2004) reported that activation in some brain regions was positively correlated with stuttering rate for males and females (e.g., the SMA and primary motor cortex), whilst activation in other brain regions was negatively correlated with stuttering rate for men but not women (e.g., left basal ganglia and right midcingulate gyrus). The Ingham et al. (2004) study demonstrated there are sex-related neural differences within PWS, which is consistent with the fact that there is a greater number of males who stutter than there are females (Drayna et al., 1999). Overall, such studies demonstrate stuttering neural activity may vary based on severity, gender and other factors across participants (e.g. handedness). This is an important consideration as tDCS modulation acts on networks engaged in a task (Peña-Gómez et al., 2012) and interacts with underlying cortical excitability and neural structure (Bestmann, de Berker & Bonaiuto, 2015). If task related neural activity, cortical excitability and neural structure vary across individuals, tDCS induced effects are consequently likely to vary across individuals. Structural variability of PWS brains as well as cortical excitability and functional neural activity may therefore have resulted in non-significant tDCS effects due to variation in neural activity and structure within PWS.

5.4.2.3 Variability of tDCS response. While the results in Chapters 3 and 4 demonstrated that tDCS can lead to improved speech production in TS, modulations of neural activity and observed behavioural effects in TS do not necessarily predict that the same effects occur in patients who present with differing neural structure, function, excitability and connectivity to fluent controls (Bola et al., 2014; Etchell et al., 2018;

Westwood et al., 2017; Woods et al., 2016). Consequently, a patient's responsiveness to tDCS may differ from that of TS. For example, Meesen et al (2014) reported that a stimulation protocol which enhanced plasticity and improved motor learning ability in TS had no effect in multiple sclerosis patients with impaired motor learning ability. Similarly, Fregni et al (2005) reported that 1 mA tDCS improved working memory in TS but the same effect was only observed in Parkinsons' patients when 2 mA tDCS was applied (Boggio et al., 2006). Furthermore, Nikolin et al. (2018) demonstrated, in a working memory task, that whilst tDCS produced significant effects for 1ma and 2ma of tDCS intensity, the greatest effect was observed at 1ma intensity. Research has also shown that the duration of stimulation delivered here (i.e. 20 minutes) is a suitable and effective duration for corticospinal excitability increases in older adults (60-76 years of age) but shorter durations may be more beneficial for younger adults (Puri, Hinder Canty & Summers, 2016). The above findings are consistent with research showing longer durations of tDCS with higher intensities may reverse the polarity of stimulation or activate homeostatic mechanisms that reduce excessive levels of neural activation, which in turn reduces or nullifies tDCS effects (Krause & Cohen Kadosh, 2014; Nitsche et al., 2003; Siebner et al., 2004). Consequently, it appears that stimulation for a duration less than 20 min for our younger participants (we had nine who were under 30 years of age) is an important parameter to look at in future work. Hence, the use of 2 mA tDCS for 20 minutes, whilst beneficial for TS as shown in Chapters 3 and 4, may have resulted in effects of tDCS being minimised due to a tDCS dose being excessive for the population being studied.

5.4.2.4 Using both online and offline tDCS. The intervention sessions lasted on average around 45 minutes, with stimulation lasting for 20 minutes. Hence our study used a mixture of online and offline tDCS. Research suggests the effects of tDCS can persist for an hour after the end of stimulation (Nitsche & Paulus, 2000). This is partially consistent with the findings of our tongue twister study in Chapter 4 that showed tDCS effects persisted for up to an hour post engaging in a challenging task alongside tDCS, but the persistence of the

effect observed in our study was not significant. However, studies report tDCS induced cortical excitability is at its highest during, rather than post, stimulation (Martin et al., 2014; Stagg et al., 2013). Hence it is possible that our results reflect the effect of tDCS only being maximally beneficial for 20 minutes and becoming progressively weaker for the rest of the intervention session. This is potentially an issue as therapy was self-paced and therefore participants may not have been engaging with the therapy in the most challenging manner in the first 20 minutes. A possible improvement to this study may be to limit the intervention to 20 minutes of intensive work, in this way intervention is always applied as an adjunct to tDCS and intensively as possible. Alternatively, 20 minutes of 'warm up' could be conducted with the less challenging stimuli before switching on tDCS during engagement with challenging stimuli in the latter half of the session. It is important to note, however, that research in TS has shown no evidence for a quantitative difference between online and offline tDCS protocols where both produce similar effect sizes (Klaus & Schutter, 2018).

5.4.2.5 Treatment intensity. A further factor that may have affected the strength of our tDCS effect is treatment intensity. Acquiring and consolidating motor skills requires intense and repetitive practice (Ludlow et al., 2008). Perhaps the results in this study reflect fewer opportunities for consolidation as participants received only five sessions over a two-week period. Thus, treatment may not have been sufficiently intensive to facilitate the behavioural changes reported in other treatment approaches for stuttering (Giraud et al., 2008; Ingham et al., 2015; Langevin et al., 2010; Neumann et al., 2005; O'Brian, Onslow, Cream & Packman, 2003). Although Andrews, Guitar and Howie's (1980) meta-analysis concluded easy onset and prolongation to be the most effective fluency-shaping techniques, the average treatment duration for these studies was 80-hours over an eight-week period. In addition, for example, although the Precision Fluency-shaping approach led to significant reductions in dysfluency during both overt reading and conversation conditions, which were broadly maintained at follow-up, this approach involved 6.5 hours of daily group therapy over three weeks (Mallard & Kelley, 1982). It is possible, therefore, that our intervention was not

intensive and long enough in duration to elicit strong tDCS effects. However, in a recent review of the stuttering therapy literature, it was concluded that the correlation between increasing the number of hours of therapy and treatment outcomes remained unclear (Baxter et al., 2015).

5.4.3 Limitations.

5.4.3.1 Poor spatial targeting of tDCS. A limitation of this study is the size of the stimulation electrode that was used. The anodal electrode was a standard 5 x 7 electrode (35cm^2 current density), placed over the LIFG (F5 on the EEG 10-20 system), with the reference placed over the right supra-orbital ridge. However, due to the size of the electrode, regions other than the LIFG were likely to be stimulated such as the premotor cortex that is part of a potential compensatory mechanism in children who recover from stuttering (Garnett et al., 2018). As regions other than the LIFG were likely to have been stimulated, the current flow may have been widely distributed and affected regions beyond the LIFG potentially including subcortical regions (Antal, Polania, Schmidt- Samoa, Dechent, & Paulus, 2011; Crinion, 2018; Polanía, Paulus, & Nitsche, 2012). This idea is supported by finite element model studies showing tDCS current spreads from the area underneath the electrode into neural tissue between electrodes (Ruffini, Fox, Ripolles, Miranda & Pascual-Leone, 2014). However, research using combined tDCS and fMRI has demonstrated that tDCS over the LIFG results in the majority of the electrical current actually being passed into the LIFG (Holland et al., 2011). This is consistent with research demonstrating that the maximum impact of tDCS is close to the stimulating electrode (Antal et al., 2012; Stagg & Johansen-Berg, 2013). Overall, due to the large anodal electrode, stimulation is likely to have affected LIFG with some current spreading to neighbouring and connected region to aid speech production. This assertion must be verified in future studies using neuroimaging, which was not used in the current study, to understand the mechanism of tDCS current spread and action within PWS.

5.4.3.2 Neuro-navigation was not used. A further limitation of our study was that neuro-navigation was not used to localise the LIFG. The commonly used EEG 10-20 or 10-10 system to localise regions was employed in our study. This system, however, may lack accuracy due to individual neural variation. Hence, the targeted region may not be stimulated accurately or effectively or equally across participants (De Witte et al., 2018). To assess the accuracy of tDCS localisation, one study used both the EEG 10-20 system and MRI guided neuro-navigation to target the left dorsolateral prefrontal cortex with tDCS (De Witte et al., 2018). It was found that neuro-navigation resulted in more latero-posterior targeting of the dorsolateral prefrontal cortex, around the middle prefrontal gyrus, compared to the EEG 10-20 system. These methods of targeting also induced significantly different electrical fields. Woods et al. (2015) further demonstrated 1 cm movement in electrode position can significantly alter the distribution of current flow in the brain, as well as the intensity of stimulation in specific brain regions. Consequently, it is possible that methods of targeting may account for individual variability of response to tDCS. If electrode placement was not consistent amongst participants, this may have contributed to the variation in treatment outcomes and size of tDCS effect across individuals.

5.4.3.3 Adaptation. PWS speech fluency may have also been improved due to adaptation to the setting, tasks, and SLTs who assessed (pre and post) and trained PWS (Chesters et al., 2017; Max & Baldwin, 2010). Furthermore, stuttering is variable across contexts (Constantinio et al., 2016) and is affected by anxiety (Toyomura et al., 2018). Hence, improvements in fluency observed in this study could partly be due to reductions in anxiety and increases in situational comfort.

5.4.3.4 Low assessment sensitivity. The SSI-3 assessment does not account for contextual variability of stuttering other than by assessing stuttering from passage reading and conversation with a researcher (Riley, 1994). The SSI-3 also does not account for the tricks and avoidances used by PWS, which can result in overtly fluent speech as a result of

avoidance of anticipated stuttered words (Blomgren, 2013). As participants become more comfortable with the person and environment, they may use fewer avoidance strategies resulting in greater overtly stuttered speech. Overall, the SSI-3 assessment and measures of overt spontaneous speaking may only provide a partial picture of stuttering severity in PWS. Alternative assessments that assess stuttering and speech motor control would be beneficial in future studies.

5.4.3.5 No follow up assessments. Our study also did not contain a maintenance programme or assess expression or maintenance of improvements over a longer period of time. The multiple session intervention study of Chesters et al (2018) suggested that positive effects of tDCS in PWS last for 6 weeks with a metronome intervention. It would have been particularly beneficial to assess whether a fluency-shaping intervention alongside tDCS resulted in similar, shorter or longer after-effects of the fluency-shaping intervention. Follow up studies are essential for future research to examine the longevity of tDCS effects and as result, suitability of the tDCS protocol for long term reduction of stuttering.

5.4.4 Future work

5.4.4.1 Additional assessments. In order to provide a more explicit insight into a PWS' stuttering severity, future work should include stuttering severity assessment across situations and contexts of varying levels of challenge, anxiety and comfort. Consequently, such variation of assessment methods should lead to varying and more realistic levels of dysfluency (Karimi et al., 2013). Situations which are likely to vary in level of difficulty, anxiety and comfort and resultant dysfluency produced include speaking with a familiar person vs. unfamiliar person, talking to a person vs. speaking alone to oneself, speaking on the phone or giving a presentation (Arenas, 2017; Vanryckeghem, Matthews & Xu, 2017). Such an approach to assessment would allow researchers to obtain a more accurate overall measure of stuttering severity across situations. As a result, a more realistic account of the

severity of stuttering being treated with the intervention can be obtained. Amir, Shapira, Mick and Yarrus (2018) recently proposed a new time domain measure of assessing speech fluency which was found to be correlated (r = 0.92) with subjective stuttering severity ratings. PWS can appear outwardly fluent due to the result of heightened awareness of stuttering and avoidance of words. Hence while a PWS may be aware they are stuttering, and avoiding doing so, a clinician may not be aware. Due to correlations with subjective stuttering severity, such a measure can provide a more accurate measure of stuttering compared to SSI-3. Future work should also use alternative assessments to assess speech motor control. Motor skill assessments such as diadochokinesis involve the rapid alternation of muscular postures, namely repetition of phonemes such as puh, tuh, kuh. Such assessments are commonly and clinically used to test a participant's articulation and control of the associated muscles (Cohen & Waters, 1999; Yang, Chung, Chi, Chen & Wang, 2011).

5.4.4.2 Use of HD-tDCS to improve focality. High definition tDCS (HD-tDCS) could be employed to overcome limitations associated with tDCS such as low focality of stimulation and consequent wide current spread. HD-tDCS consists of an active electrode, which is smaller than a traditional tDCS electrode, being surrounded by multiple return electrodes, usually in a 4x1 montage (Alam et al., 2014; Datta et al., 2009; Edwards et al., 2013; Ruffini et al., 2013). Due to the montage arrangement, stimulation is applied with a greater level of spatial accuracy compared to tDCS (Dmochowski et al., 2013). The increased focality afforded with HD-tDCS, stimulation therefore results in greater electric field generation within the cortex, as well as greater and prolonged motor evoked potential (MEP) amplitudes compared to tDCS (Kuo et al., 2013; Muthalib et al., 2017). HD-tDCS may therefore be a preferable method in future studies over traditional tDCS due to increased focality and specificity of stimulation.

5.4.4.3 Alternative Stimulation Protocols. The tDCS montage and stimulation parameters used in this study were chosen as they have previously been shown to be

effective for modulating speech motor learning and rehabilitation in previous research with aphasia (Allman et al., 2016; Marangolo et al., 2011) and in our studies with TS described in Chapters 3 and 4. An alternative tDCS montage that may lead to stronger effects involves the targeted region first being inhibited via cathodal stimulation, and then excited using anodal stimulation to enhance anodal tDCS effects (Christova et al., 2015; Fujiyama et al., 2017). In two studies, priming with cathodal tDCS (1 mA during 15 min and 1.5 mA during 10 min, respectively) reduced cortical excitability (reduced MEP amplitude and ICF) and increased cortical inhibition. After anodal tDCS, participants showed greater skill improvement and corticospinal excitability increases compared to participants who did not receive cathodal priming stimulation. Hence, preconditioning the targeted neural area with cathodal tDCS could result in enhanced effects of anodal tDCS. Cathodal tDCS could also be used to inhibit the overactive RIFG, a region thought to be involved in stuttering compensation and in which neural activity has been shown to scale with stuttering severity (De Nil et al., 2003; Kell et al., 2009; Lu et al., 2009; Neef et al., 2018; Sommer et al., 2002; Watkins et al., 2008). Such a stimulation protocol could be effective by down-regulating the inhibition of the RIFG whilst engaging the LIFG. Alternatively, this approach could be efficacious for facilitating recruitment of perilesional areas (around the impaired LIFG) by decreasing the impact of inhibition in these areas (Aguiar et al., 2015; Hamilton et al., 2011). This approach has been successful at reducing symptoms in aphasia interventions (Jung et al., 2011; Monti et al, 2008; Otal et al., 2015; You et al., 2011). Cathodal stimulation over the RIFG could be applied either in a unipolar montage or bipolar montage alongside anodal LIFG tDCS to promote a lateralisation shift back to the left hemisphere to facilitate language recovery (Jung et al., 2011; Kang et al., 2011). However, research with PWS suggests that right hemisphere overactivity is a characteristic of compensating for stuttering (Etchell et al., 2018). Therefore, inhibiting the RIFG could potentially lead to an increase of stuttering.

5.4.4.4 Alternative Regions of Interest. As explored in the literature review in Chapter 2, speech production involves timely coordination within a network of cortical and

subcortical regions. The LIFG was chosen as our region of interest because of indications that this region is involved in stuttering severity reduction (Neef et al., 2016) and can be used to improve speech processes in aphasic patients (Marangolo et al., 2013) and TS (Fiori et al., 2014). However, numerous other cortical and subcortical regions have been implicated in stuttering, indicating stuttering is a network level dysfunction which results in dysfluency rather than a single region dysfunction (Etchell et al., 2018; Neef et al., 2018). For example, fMRI studies show picture naming tasks result in activation of a large fronto-temporal network in left and right hemispheres such as the superior temporal gyrus, middle temporal gyrus and anterior temporal lobe (Abel et al., 2011; Heath et al., 2012; Indefrey, 2011; Price, 2012). Such regions have been shown to be dysfunctional in PWS (Etchell et al., 2018) and may therefore be valid targets for stimulation studies seeking to improve fluency in PWS.

Sitek et al (2016) found connections between the orbitofrontal cortex and subcortical regions such as the basal ganglia were negatively correlated with stuttering severity. Whilst the cerebellum is difficult to target with tDCS and often painful, the orbitofrontal cortex is a cortical region that could potentially be targeted with tDCS to reduce stuttering severity. Kell et al. (2017) found that stuttering recovery reduced hyper-connectivity of somatosensory feedback between the left supramarginal gyrus and the prefrontal cortex. Recovery also increased auditory-motor connectivity between auditory feedback processing superior temporal gyrus and the articulatory motor cortex. Stimulation of nodes within these networks shown to be responsible for stuttering recovery therefore may be further targets for stimulation studies in PWS. Future work requires direct comparison between protocols targeting differing regions associated with impairment and recovery in PWS to determine optimal parameters for tDCS intervention.

5.4.4.5 Use of Neuroimaging. Neuroimaging can be used in future studies for neuro-navigation purposes, allowing control over low spatial accuracy of targeting stimulation regions in tDCS studies (De Witte et al., 2018). Neuro-navigation ensures more

homogenous positioning of electrodes over regions of interest, and consequently more homogeneity in the induced current fields. Crucially, use of neuroimaging in future tDCS intervention work with PWS is essential for understanding tDCS and fluency enhancement mechanisms. Polanía, Nitsche and Ruff (2018) suggested that tDCS studies which only acquire behavioural data are the most exploratory and least conclusive and are likely to have high levels of variability in effect size. This is due to the fact that attempting to understand the functionality of a given region, without considering the wider networks it engages, makes it difficult and near impossible to fully understand tDCS effects. As we did not employ brain imaging in our study to assess tDCS and intervention effects, it is not possible to determine the neuro-mechanistic reasons for our results. Improvements in fluency observed in PWS may have been due to increased or decreased activity in the LIFG or non-focal interconnected regions. By acquiring brain imaging data for PWS, we can unpick the relationship between intervention approach and fluency, and moreover the factors contributing to high, moderate and low response to tDCS. This would allow better understanding of the mechanisms behind dysfluency and tDCS based intervention in PWS. The excellent temporal resolution of EEG for example offers the potential to assess how neural responses to tDCS change throughout the stimulation period within an area or across networks (Bortoletto et al., 2014; Miniussi et al., 2012).

5.4.5 Summary. Overall, our study demonstrated reductions in stuttering severity in PWS (trending towards significance), after a multiple session fluency-shaping intervention delivered concurrent with LIFG anodal tDCS (2ma, 20 minutes). A second group of PWS who received the same intervention concurrent with sham tDCS showed comparatively smaller non-significant improvements in stuttering post intervention. Our results indicate the potential for tDCS to reduce stuttering and enhance current clinical interventions. Further research is required for optimisation and enhancement of tDCS effects with research that utilises different types of intervention and target sites; recruits larger samples of PWS with more homogenous levels of severity; and uses neuroimaging to understand the mechanisms

of tDCS effects and underlying mechanisms of stuttering variability. As tDCS is low cost, simple to use and requires minimal training, it is a tool of vast potential clinical value. With further research and optimisation of effects, tDCS could lead to enhancement of clinical interventions in PWS and significant reduction of stuttering severity.

Chapter 6: Exploring the neural basis of stuttering during conversation using fNIRS

6.1 Introduction

In Chapter 5, we used anodal tDCS over the LIFG in PWS alongside a challenging fluency shaping intervention to assess if this method could reduce overt stuttering. We observed that the anodal tDCS group displayed greater reduction of stuttering severity compared to the sham tDCS group, although these differences were not significant. This was deemed to be largely due to the small sample size available for the experiment and the high degree of variability of stuttering across participants. However, we observed reduction in stuttering severity that was trending towards significance on the conversational stuttering severity assessment in our experiment. Conversation is an ecologically valid outcome measure that reflects real world situations. Importantly, no previous study has assessed the neural mechanisms of stuttering in the context in which we observed reduction of stuttering following tDCS i.e. natural connected speech during a face-to-face conversation with another person. It is important to understand such neural mechanisms as the effects of tDCS in reducing stuttering in PWS may be enhanced and refined. This is of acute importance as tDCS current interacts with underlying brain activity in targeted networks to produce its effects. Hence it is important to understand the mechanism of stuttering within ecologically valid contexts in order to deliver therapeutic effects that are transferrable to real world settings and to enhance positive effects of tDCS interventions on ecologically valid outcome measures such as conversation. Consequently, in this chapter, we present an fNIRS study that aimed to assess LIFG neural activity in a face-to-face social interaction task with some similarities with what happens in interventions like that employed in Chapter 5.

Although there has been significant neuroimaging work investigating stuttering over the past 20 years, our understanding of the stuttering brain remains unclear and incomplete (Etchell et al., 2018). As outlined in Chapter 2, research has revealed that there are many neural regions of structural and functional dysfunction in PWS (Brown et al., 2005; Etchell et al., 2018). Although there is no agreement with respect to the functional mechanisms of stuttering, research does suggest the LIFG plays a crucial role in typical speech production

and stuttering (Neef et al., 2016), particularly speech motor preparation (Flinker et al., 2015) and timing (Long et al., 2016).

However, previous functional neuroimaging studies with PWS have largely been constrained to abstract fMRI speech production paradigms such as choral, single word and sentence reading (Belyk et al., 2015; Budde et al., 2014; Etchell et al., 2018; Fox et al., 1996; Kell et al., 2009; Neef et al., 2015; Neumann et al., 2005; Watkins et al., 2008; Wu et al., 1995). Whilst experimental control in these studies is high, the studies themselves lack ecological validity and neglect to assess stuttering in the contexts in which it occurs in the real world or with naturalistic connected speech as stimuli. A likely reason for this gap in previous research is that methodological restrictions of some neuroimaging equipment do not allow for naturalistic assessments, e.g. during face-to-face conversation, to take place.

Previous functional neuroimaging studies with PWS have used a variety of methods to assess neural activity in PWS (Quaresima & Ferrari, 2016) such as fMRI (e.g. Watkins et al., 2008), PET (e.g. Wu et al., 1995), EEG (Vanhoutte et al., 2015) and MEG (e.g. Sowman, 2014). All of these measures either do not allow measurement in face-to-face settings or they do not allow measurement of neural activity related to long utterances of natural connected speech. For example, fMRI is currently the most widely used neuroimaging method. However, this method is limited in that it requires one to lie inside an MRI scanner; it produces high levels of scanning noise and is susceptible to movement artefacts. As such, fMRI studies of speech production typically use short word or sentence reading tasks or use imagined continuous speech production tasks. Our current knowledge of stuttering is, therefore, largely built on studies in speech production that have used artificial environments and stimuli. Neuroimaging technology that allows for the assessment of neural signals across naturalistic contexts as well as with naturalistic stimuli (i.e. connected speech) is, therefore, essential for extending our understanding about the mechanisms of stuttering and consequently developing effective interventions using brain stimulation methods. One method that allows assessment of neural activity within naturalistic contexts is fNIRS.

No study to date has examined neural activity in PWS within naturalistic contexts and conversations. Toyomura et al. (2018) attempted to address this issue by conducting an experiment involving live communication with a stranger during fMRI using a video link. In one condition, the stranger looked at the participant without speaking whereas in the live condition, the stranger asked questions that the participant was required to answer. It was found that activity in the right amygdala, a region implicated in emotional processing, was significantly correlated with stuttering in PWS. Activity in the prefrontal cortex, which forms emotion regulation neural circuitry when it is coupled with the amygdala, was decreased in PWS compared to controls. Activity within the LIFG was also significantly lower compared to TS. Such research with PWS involving conversational and face-to-face tasks therefore demonstrates how naturalistic paradigms can add to our understanding of stuttering. However, despite involving face-to-face communication, the study by Toyomura et al. (2018) lacked ecological validity as it was conducted inside an MRI scanner. Furthermore, naturalistic speech was elicited but was limited to short and relatively automatic utterances e.g. “What is your name?” Hence, it would be beneficial to assess speech activity in PWS using a connected speech task that allows for longer naturalistic utterances as well as in face to face communication with a person. fNIRS is a method that permits such experiments to be conducted.

fNIRS is a non-invasive method that uses near-infrared light (across 650-900 nm wavelengths) to measure changes in oxygenated and deoxygenated haemoglobin concentrations within the cortex. In addition, comparative studies have demonstrated fNIRS signals have strong concordance with fMRI signals (Gervain et al., 2011). However, fNIRS has its own limitations such as low spatial resolution and inability to assess activity beyond surface level cortical areas. Despite these limitations, fNIRS is a versatile neuroimaging method due to it being non-invasive, low cost, portable, resistant to movement artefacts, and allowing for neural activity to be assessed within naturalistic situations using naturalistic stimuli (Huppert et al., 2009).

Two previous studies have examined neural activity within TS during a face-to-face social interaction, with a connected speech task, using fNIRS (Suda et al., 2010; 2011). In Suda et al. (2010), results showed that the social conversation condition (15 second turns of speaking face to face with a researcher) resulted in increased activation within social cognition areas such as the superior frontal and superior temporal gyri compared to a control task of reciting meaningless syllables. The LIFG did not show significantly greater activity within the social condition, due to the control condition involving only performing a phonation task. Suda et al. (2011) further conducted a similar study assessing prefrontal cortex and superior temporal sulcus activity in relation to autistic traits in TS. Prefrontal cortex and superior temporal sulcus activity was significantly greater during face-to-face conversations compared to a control condition. Such studies therefore demonstrate that fNIRS can be used to examine neural activity during face-to-face conversational tasks.

Only two previous published studies have used fNIRS to examine neural activity in PWS. Sato et al. (2011) used fNIRS to measure auditory speech processing across children and adults who stutter and found reduced left hemisphere neural activity during processing of phonemes compared to processing prosodic stimuli. The severity of stuttering was further correlated with right hemisphere activity during phonemic contrast trials. Walsh et al. (2017) explored neural responses associated with fluent speech production in children who stutter using a naturalistic connected speech task (picture description). Children who stutter displayed deactivation of the LIFG and left premotor cortex compared to fluent children. These results were consistent with the findings of recent meta analyses reported by Budde et al. (2014) and Belyk et al. (2015). Overall, fNIRS has only been used in a limited way to examine neural activity in PWS, with no studies examining speech production in naturalistic contexts with naturalistic stimuli.

Therefore, this study used fNIRS to examine neural activity in PWS and TS during an in-person face-to-face interaction task, with naturalistic connected speech stimuli. We examined neural activity within the LIFG as our tDCS study in Chapter 5 indicated anodal stimulation during intervention led to reductions in conversation stuttering severity that were

trending towards significance. Similar stuttering severity reductions were observed in conversation in Chesters et al. (2018), who also used tDCS over the LIFG alongside an intervention to treat stuttering. Furthermore, the LIFG is consistently shown to be a region of dysfunction in PWS (Etchell et al., 2018) but neural activity has not been assessed in PWS in face-to-face interactions involving connected speech. In addition to the LIFG, we also assessed neural activity within the homologous RIFG that shows over activation in PWS compared to TS (Belyk et al., 2015; Brown et al., 2005; De Nil et al., 2008; Lu et al., 2009; Neef et al., 2016; Neumann et al., 2005; Watkins et al., 2008). This over activation is thought to be compensatory in nature due to deficits in LIFG connections with motor areas in PWS (Chang et al., 2008; Kell et al., 2009; Lu et al., 2009; Sommer et al., 2002; Sowman et al., 2014; Watkins et al., 2008).

Within our study, two speaking conditions were used: Social Conversation (speaking in turn face to face with a researcher) and Audio Conversation (speaking in turn with pre-recorded audio of a researcher speaking, with no researcher present). The Audio Conversation condition was used as a contrast in order to examine the difference in neural activity during conversation when face to face with a person vs. speaking alone in a simulated conversation. This was of importance as our improvement in stuttering severity in Chapter 5 was strongest in the conversation condition, which involved face-to-face naturalistic conversation. Hence, contrasting Social Conversation and Audio Conversation was expected to give insight into the possibly unique neural activity patterns in PWS during face-to-face interactions, which may have interacted with, and contributed to, the stuttering severity reduction observed in Chapter 5. Furthermore, understanding the difference in neural mechanisms in PWS between social and non-social situations, using ecologically valid conditions and stimuli, may be key to understanding the mechanisms behind stuttering in real world social situations. As such, this knowledge could be used to develop interventions for which effects are transferable and generalisable outside of clinical settings, which is a significant limitation of current stuttering therapy approaches (Baxter et al., 2016). We did not specify a directional hypothesis, as this was the first study of its kind. Hence, we

hypothesised that speech production neural activity within the LIFG and RIFG would differ significantly compared to TS in both the Audio Conversation and Social Conversation conditions of our task.

6.2 Method

6.2.1 Participants. Twenty PWS (age range: 20-51; mean age: 29.5; SD: 9.91) and 20 TS (age range: 18-47; mean age: 23.6; SD: 6.97) were recruited. TS were recruited through the UCL SONA participant recruitment system and PWS were recruited from the UCL Stuttering Self-Help Group and personal contact. Participants also met further inclusion criteria: no speech, language, or communication disorder besides stuttering (PWS group only), no sensory impairment, no history of neurological or physical disease, no history of drug abuse or taking of prescribed medication in the last six months. All participants provided full informed consent. All procedures were approved by the UCL Department of Psychology Ethics Committee.

6.2.2 Design. A 2 (Hemisphere; RIFG and LIFG) x 2 (Group; TS and PWS) x 2 (Condition; Audio Conversation and Social Conversation) mixed factorial design was used. Neural activity in the LIFG and RIFG were recorded using fNIRS during conversation conditions. Speech fluency data were measured for both PWS and TS to assess total number of syllables produced, stuttered and percentage of syllables stuttered. Stuttered syllables were denoted as repetitions and prolongations of phonemes or syllables, hesitations and blocks. Interjections, repetitive multisyllabic words or phrases were not counted. Counterbalancing of conversation conditions was performed.

6.2.3 Task and materials. Participants engaged in two conversation-style speaking conditions: Social Conversation (speaking face to face with a researcher) and Audio Conversation (conversing with an audio recording of an interlocutor). Each condition lasted about 14-15 minutes in total and began with a 1-minute silent rest period to allow the

participant to acclimatise to the testing environment. Each condition consisted of 10 trials in four stages that lasted for 20 seconds each (Figure 12). The stages were as follows:

Stage 1 – Listen (20 seconds): A 500ms beep was followed by a conversational question (e.g. “What are you looking forward to this week?”) voiced by the researcher. Thirty-three prompts were employed. Three were used for practice trials and were excluded from analyses. Twenty questions were selected at random from the pool of 30 with equal numbers for the Audio and Social Conversation conditions. The interlocutor said their name at the beginning of each trial and then asked a question and gave their own response to this question. These conversational questions and answers were either delivered face to face (Social Conversation condition) or pre-recorded (Audio Conversation).

Stage 2 – Rest (20 seconds): A 500ms beep signalled the start of the rest phase, where the participant had to remain silent.

Stage 3 – Speak (20 seconds): Two 250ms beeps indicated that it was the participant’s turn to begin speaking. Participants stated their name and the response to the question they had just heard.

Stage 4 – Rest II (20 seconds): Five 100ms beeps signalled that the participant should stop speaking and rest. The participant was required to remain silent in this period.

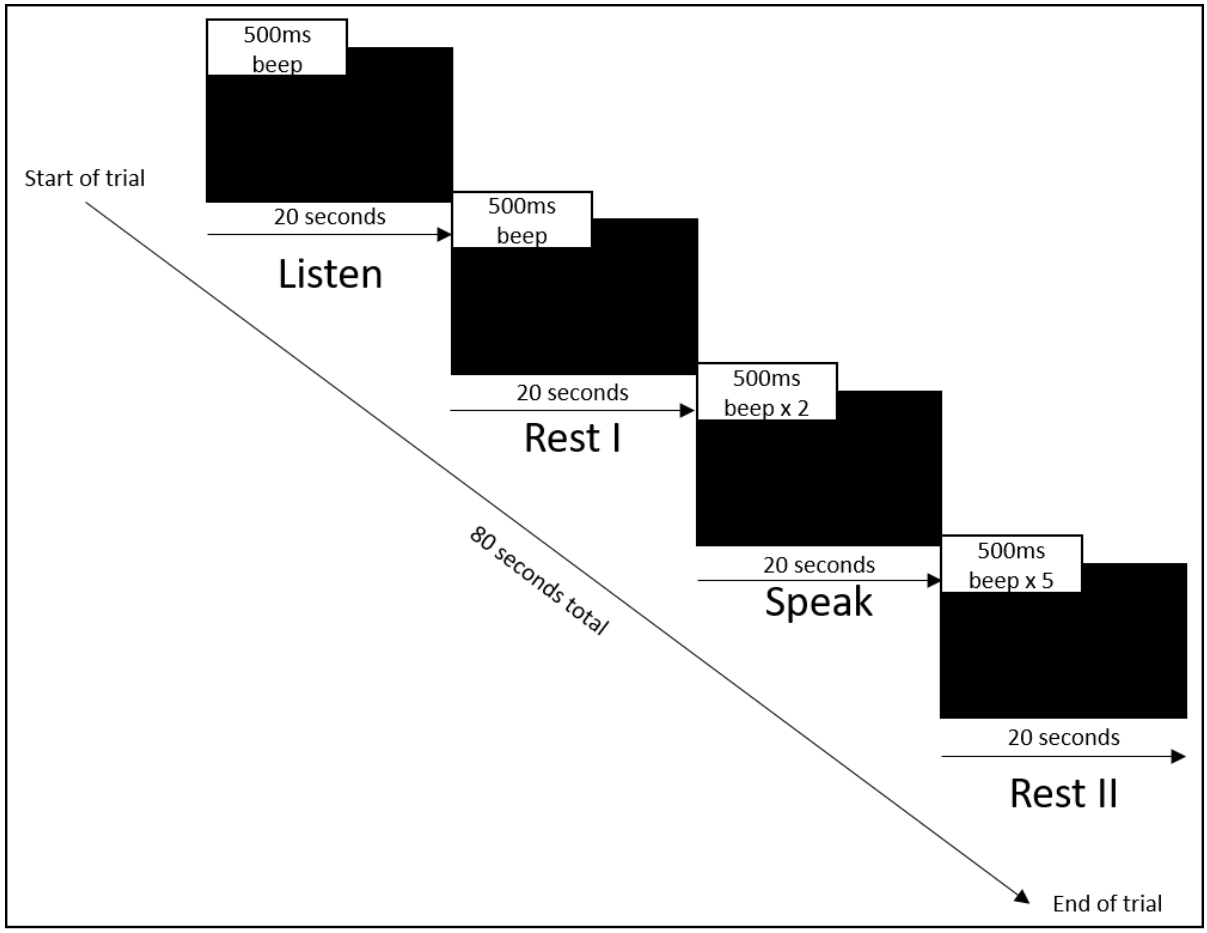

Figure 19. The experimental sequence showing the four 20 second stages of a trial

Figure 19 depicts an example trial from the Audio Conversation condition, where the screen was blank for the duration of the experiment. For the Social Conversation condition, a text prompt was displayed in the Listen stage that was read aloud by the researcher. The computer screen was tilted away from the participant during this condition, so participants could not read the question.

Participants' speech was recorded throughout using a USB microphone and Audacity software. Participants were aware that they were being recorded but were informed that researchers outside the test room could not hear them speaking.

6.2.4 fNIRS. A Hitachi ETG-4000 Optical Topography system (Hitachi Medical Corporation, Kashiwa, Japan) was used to obtain fNIRS data during conversation conditions. Haemodynamic fluctuations were obtained from 44 fNIRS channels (Figure 20) split across two 3x5 optode holders (3cm distance between each optode). This resulted in 22 fNIRS channels per hemisphere. The optode holders were fitted inside an elastic cap that was placed on the participant's head. Optode holders of this size were used to provide adequate coverage of our channels of interest (9, 13, 18 and 22 LIFG; 27, 36, 41 RIFG) and simple placement and alignment on a participant's head. The size of these optode holders resulted in fNIRS data being collected for regions beyond our ROI's. Only the data for our ROI's were analysed and reported in this chapter.

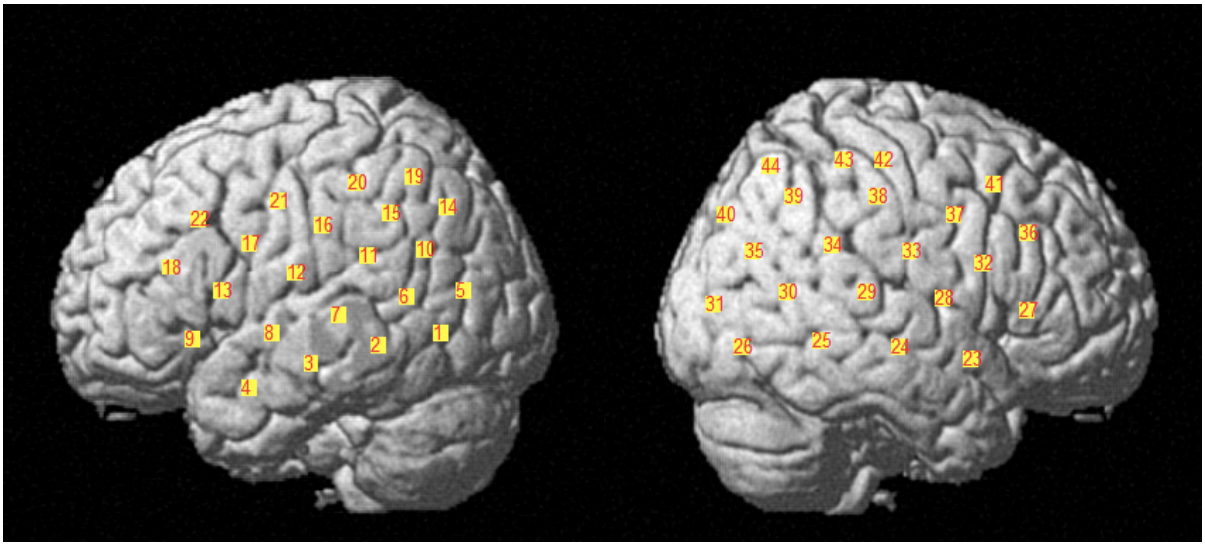

Figure 20. fNIRS optode channels corresponding to the Montreal Neurological Institute brain template. Channels 9, 13, 18 and 22 corresponded to the LIFG whereas channels 27, 36 and 41 corresponded to the RIFG.

6.2.5 Procedure. The procedure was explained to participants who then completed a screening questionnaire and signed a consent form. Participants were asked to remove any metal from their person and place it outside the room to avoid interference with the

PATRIOT (Polemus, Vermont) magnetic digitiser used during fNIRS set-up. Participants read task instructions for the practice condition from a computer screen. Participants were left alone in the testing room during the three practice trials (these were from the Audio Conversation condition). Task requirements did not change between conditions hence practice under the Social Conversation condition was not necessary. Once practice trials were complete, researchers re-entered the room and began fNIRS setup.

Anatomical landmarks (left and right pre-auricular points, nasion, inion and Cz) were located using a tape measure and locations were marked with coloured stickers that were used for reference when digitising optode positions. The fNIRS cap had the optodes pre-placed and this was positioned on the participant's head. Each optode was then removed, and the hair beneath the optode was parted to expose the participant's scalp. This ensured good contact between the optode and the scalp and gave good signal quality. Signal quality of the fNIRS optode array was then checked using the AutoGain function of the Hitachi ETG-4000. Further adjustments of the hair were made when necessary. Once all the channels had low signal to noise ratio, digitising began using the PATRIOT (Polemus, Vermont) magnetic digitising system. Anatomical landmarks and optode positions were digitised in standard 10-20 space.

The order of Audio Conversation and Social Conversation conditions were counterbalanced across participants. The procedure for the Audio Conversation condition was identical to that described for practice trials. For the Social Conversation condition, the interlocutor sat opposite the participant behind the computer screen which faced the participant. There was a 10-minute break between sessions where the fNIRS cap was removed to relieve pressure on the participant's head. The fNIRS cap was replaced onto the participant's head and channels were checked and adjusted as necessary. Once the experiment was completed, the fNIRS cap was removed and participants were debriefed.

6.2.6 fNIRS analysis. Data were first visually inspected using Homer2 (Huppert, Diamond, Franceschini & Boas, 2009). Noisy ROI channels with poor signal quality (i.e. due

to hair lying between the optode and scalp or optode scalp decoupling during the experiment) were excluded from analyses (10 LIFG and 7 RIFG in PWS; 14 LIFG and 4 RIFG in TS). Data were then pre-processed using Homer2 (version 2.2). The raw fNIRS haemoglobin intensity data were first converted into optical density data. A band-pass filter was then applied to remove physiological artefacts (such as heartbeat) from the data (high pass = 0.01 Hz; low pass = 0.5 Hz). Motion artefacts were detected and removed using wavelet-based filtering (interquartile range = 0.1). The cleaned optical density data were then converted to oxygenated- (Oxy-HB) and deoxygenated- (Deoxy-HB) haemoglobin concentration values using the modified Beer-Lambert law (Huppert et al., 2009). Block averages were then obtained from 0 – 25s post stimulus onset for each fNIRS channel in the Speak and Rest II conditions to obtain the mean haemodynamic response function. The 25s duration was chosen to capture the full fluctuation of the haemodynamic response within a trial. Mean peak amplitudes of Oxy- and Deoxy-HB were obtained from participants' mean haemodynamic response function for all channels. Channels were then grouped together and averaged to form the LIFG and RIFG ROIs. Total haemoglobin levels in each ROI for the Speak and Rest II phases of each condition were calculated by subtracting Deoxy-HB from Oxy-HB. Total haemoglobin associated with speech production was then obtained by subtracting Rest II total haemoglobin values from Speak total haemoglobin values in each condition for each ROI. This final differential speech production haemoglobin level (D-Hb) was the value used in statistical analyses. Greater D-Hb values indicate stronger neural activity. The fNIRS data for TS 19 and 20 in the Audio Conversation condition were corrupted and were thus excluded from further analysis. Therefore, there were 18 TS in the Audio Conversation analyses.

6.2.7 Fluency analysis. Audio recordings of speech during the conversation conditions were transcribed and analysed manually. The total number of syllables produced, stuttered and the percentage of syllables stuttered were calculated for every trial in each conversation condition across both PWS and TS. The responses which classified as

stuttered syllables are described in 6.2.2. Auditory data for 10 (out of 40) participants were analysed twice, allowing a one-way random intraclass correlation reliability analysis. Intra-rater reliability (ICC = .949) and inter-rater reliability (ICC = .932) were high.

6.2.8 Statistical analysis. Speech fluency data were analysed using independent samples t-tests to compare the mean difference of total syllables produced during the task and percentage syllables stuttered during the task between PWS and TS. For individual channel-based analysis, mixed ANOVA's were conducted for every channel with participant group (TS vs. PWS as a between-subject factor) and Audio Conversation and Social Conversation condition as a within-subject factor. For ROI analysis, fNIRS D-Hb values were analysed using mixed ANOVA with participant group (TS vs. PWS as a between-subject factor) and Audio Conversation and Social Conversation condition as one within-subject factor and hemisphere (RIFG and LIFG) as another within-subjects factor. Significant effects were followed up paired and independent samples t-tests.

6.3 Results

6.3.1 Total syllables. An independent-samples t-test was conducted to compare the total number of syllables produced by TS and PWS across conversation conditions. As descriptive statistics shown in Table 24 and plotted in Figure 21 illustrate, PWS (mean: 535.75, SD: 257.09) produced significantly fewer syllables compared to TS (mean: 702.50, SD: 209.98) in the Audio Conversation condition, $t(38) = -2.246$, $p = .031$. PWS (mean: 520.55, SD: 264.44) also produced significantly fewer syllables compared to TS (mean: 747.95, SD: 189.44) in Social Conversation condition, $t(38) = -3.134$, $p = .003$. Further paired samples t-tests showed the difference in number of syllables produced across Audio Conversation and Social Conversation conditions was not significant for both PWS ($t(19) = .200$, $p = .843$) and TS ($t(19) = -.804$, $p = .432$).

Table 24.

Mean (SD) total number of syllables produced by PWS and TS across Audio and Social Conversation conditions

	Audio Conversation	Social Conversation
PWS	535.75 (257.09)	520.55 (264.44)
TS	702.50 (209.98)	747.95 (189.44)

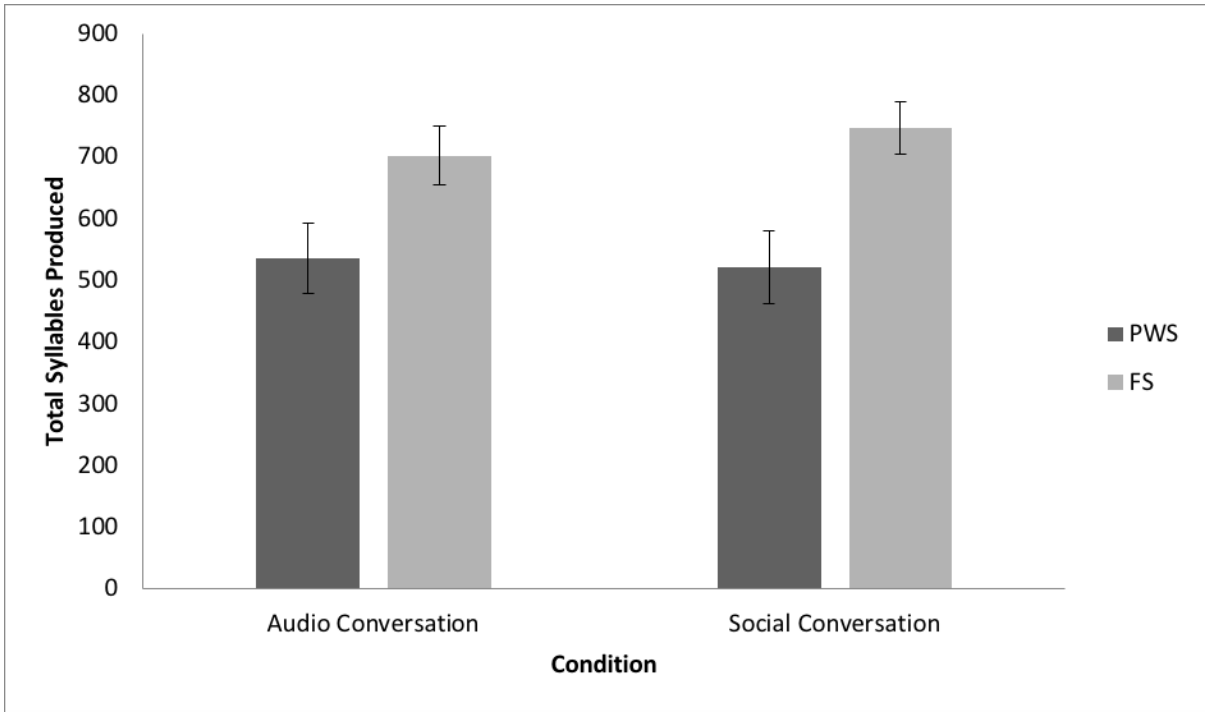

Figure 21. Total number of syllables produced in the audio and social conversation conditions for PWS and TS. Error bars represent +/- one standard error.

6.3.2 Syllables stuttered. An independent-samples t-test was conducted to compare the percentage of syllables stuttered across conversation conditions by TS and PWS. As detailed in Table 25 and plotted in Figure 22, PWS (mean: 8.91%, SD: 12.76%) displayed a significantly greater percentage of syllables stuttered compared to TS (mean: 1.79%, SD: 2.32) in the Audio Conversation ($t(38) = 2.452$, $p = .019$). PWS (mean: 11.02%, SD: 17.08%) also displayed a significantly greater percentage of syllables stuttered

compared to TS (mean: 1.84%, SD: 2.19%) during the Social Conversation conditions (t (38) =2.383, p = .022). Further paired samples t-tests showed that the difference in percentage syllables stuttered between Audio and Social conversation conditions was not significant for both PWS (t (19) = -1.414, p = .174) and TS (t (19) = -.074, p = .942).

Table 25.

Mean percentage (SD) of syllables stuttered by PWS and TS across Audio and Social Conversation conditions

	Audio Conversation	Social Conversation
PWS	8.91% (12.76)	11.02% (17.08)
TS	1.79% (2.32)	1.84% (2.19)

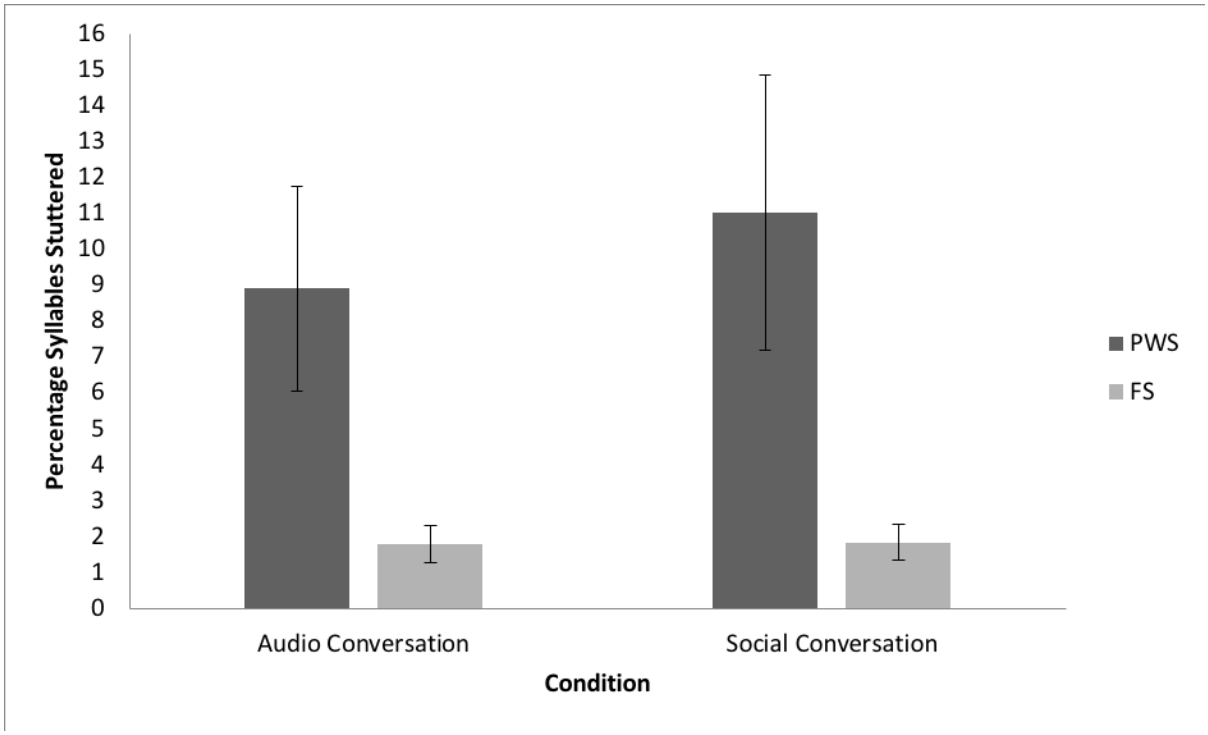

Figure 22. The percentage of syllables stuttered across audio and social conversation conditions for PWS and TS. Error bars represent +/- one standard error.

In summary, the speech fluency data showed that overall, PWS produced significantly fewer syllables and significantly greater dysfluency compared to TS across conversation conditions. In addition, both PWS and TS did not produce significantly different total number of syllables produced or percentage of syllables stuttered between Audio Conversation and Social Conversation conditions.

6.3.3 fNIRS channel analysis. For individual channel-based analyses, mixed ANOVA's were used for every channel to assess the effect of the conversation condition on D-Hb within the LIFG and RIFG channels between PWS and TS. There was a marginally significant main effect of condition ($F(1, 36) = 3.372$, $p = .075$) for Channel 9 (in the LIFG), indicating greater LIFG activation in the Social Conversation condition (mean: .216, SD: .359) compared to the Audio Conversation condition (mean: .027, SD: .453).

There was also a significant interaction between the effect of condition and participant group for this channel ($F(1, 36) = 5.088$, $p = .030$), indicating PWS and TS had significantly different levels of LIFG activity across the two conversation conditions.

There were no main effects or interactions for any other channel in the left (Table 26) or right (Table 27) hemispheres. Independent samples t-tests were then used to follow up the significant effects to compare levels of D-Hb between PWS and TS across Audio and Conversation Speaking conditions for LIFG and RIFG channels.

Table 26.

Results of LIFG channel-based ANOVA's for PWS and TS, df = 36

	***F*-value**	***p*-value**
Ch9Condition	3.372	.075
Ch9Condition*Participant	**5.088**	**.030**
Ch13Condition	.807	.375
Ch13Condition*Participant	.974	.330
Ch18Condition	.287	.595
Ch18Condition*Participant	2.153	.151
Ch22Condition	1.679	.204
Ch22Condition*Participant	.441	.511

Table 27.

Results of RIFG channel-based ANOVA's for PWS and TS, df = 36

	***F*-value**	***p*-value**
Ch27Condition	.429	.517
Ch27Condition*Participant	.582	.451
Ch36Condition	1.354	.252
Ch36Condition*Participant	.845	.364
Ch41Condition	.031	.861
Ch41Condition*Participant	.470	.498

Results of the independent samples t-test showed PWS (mean: .373, SD: .230) had significantly greater D-Hb values, and therefore LIFG activation, compared to TS (mean: -.022, SD: .44921) in Channel 9 in the Social Conversation condition, t (38) = 3.507, p = .001. Results also showed PWS (mean: .207, SD: .322) had higher D-Hb levels, and LIFG activation, compared to TS (mean: -.023, SD: .413) in Channel 13 in the Social Conversation condition, an effect which was marginally significant, t (38) = 1.969, p = .056. There were no other significant differences between PWS and TS across Audio Conversation (Table 28) and Social Conversation (Table 29) conditions in the LIFG and RIFG.

Channel 9 is in the centre of the LIFG. It showed a respectable interaction with conditions and a marginal main effect across conditions in the ANOVA (Figure 23). It also significantly greater activity in the Social Conversation than the Audio Conversation conditions in independent t test analyses. Since channel 9 is located in the LIFG, ROI analyses were conducted that compared this location with RIFG.

Table 28.

Results of LIFG and RIFG channel-based Independent Samples t-tests for PWS and TS for the Audio Conversation condition. Df = 36, because of the exclusion of the data of two TS in this condition due to data corruption

Channels	***t*-value**	***p*-value**
Ch9 LIFG	-.691	.494
Ch13 LIFG	1.176	.247
Ch18 LIFG	-.956	.346
Ch22 LIFG	1.1563	.127
Ch27 RIFG	.906	.371
Ch36 RIFG	-.257	.799
Ch41 RIFG	.997	.326

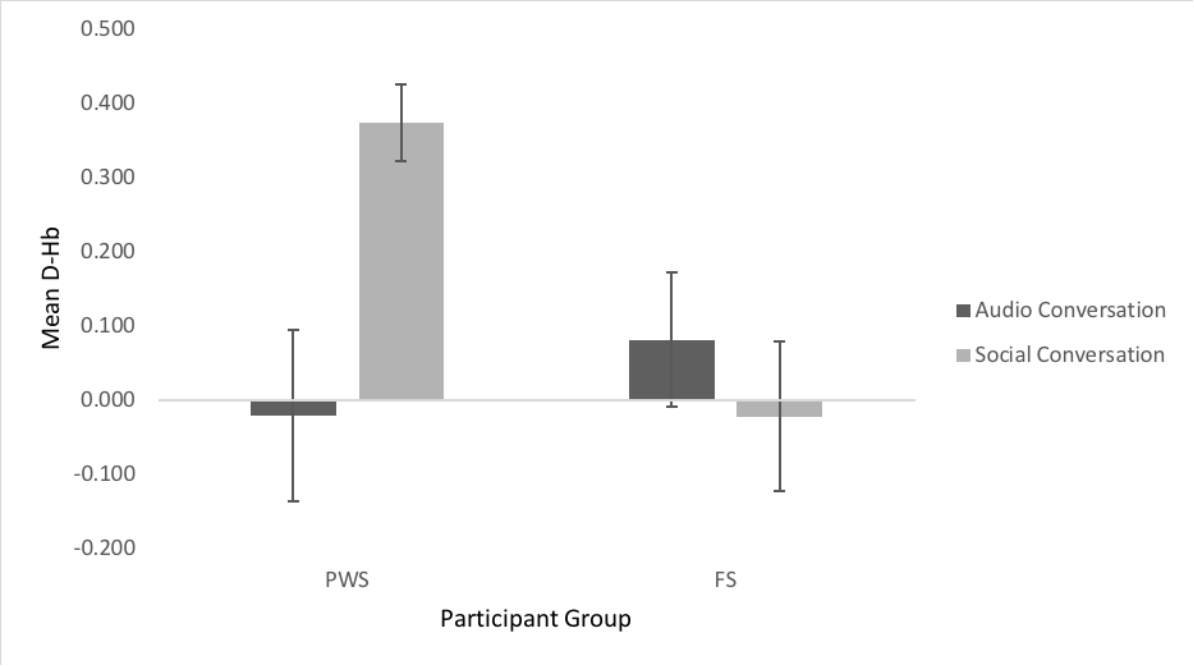

Figure 23. Mean D-Hb values for channel 9 of the LIFG within the Audio Conversation and Social Conversation conditions between PWS and TS. Error bars represent +/- one standard error.

Table 29.

Results of LIFG and RIFG channel-based Independent Samples t-tests for PWS and TS for the Social Conversation condition, df = 38

Channels	*t*-value	*p*-value
Ch9 LIFG	**3.507**	**.001**
Ch13 LIFG	**1.969**	**.056**
Ch18 LIFG	1.134	.264
Ch22 LIFG	.743	.462
Ch27 RIFG	1.705	.096
Ch36 RIFG	.651	.519
Ch41 RIFG	.576	.568

6.3.4 ROI analysis. A mixed ANOVA was used to assess the effect of the conversation condition on D-Hb within the LIFG and RIFG between PWS and TS. There was a significant main effect of Hemisphere ($F(1, 36) = 16.218$, $p<.001$), indicating reduced overall activity in the left hemisphere (mean: -.252, SE: .026) compared to the right hemisphere (mean: -071, SE: .036). However, there was no significant interaction between Hemisphere and participant group ($F(1, 36) = .492$, $p = .488$), indicating neural activity was not significantly different across PWS and TS between the LIFG and RIFG.

In addition, there was a significant main effect of Condition ($F(1, 36) = 124.187$, $p<.001$), indicating neural activity was greater in the Social Conversation (mean: .074, SE: .028) condition than in the Audio Conversation (mean: -.396, SE: .033) condition. There was also a significant interaction between Condition and participant group ($F(1, 36) = 10.605$, $p = .002$) which showed PWS (mean: -.437, SE: .045) had reduced activation compared to TS (mean: -.354, SE: .047) in the Audio Conversation condition, and increased neural activation (mean: .169, SE: .039) in the Social Conversation compared to TS (mean: -.022, SE: .041).

Furthermore, a significant interaction between Hemisphere and Condition was observed ($F(1, 36) = 27.996$, $p < .001$), indicating neural activity was greater in the right hemisphere (mean: -.202, SE: .046) in the Audio Conversation condition compared to left (mean: -.589, SE: .041), and was greater in the left hemisphere (mean: .086, SE: .036) in the Social Conversation condition compared to right hemisphere (mean: .061, SE: .047). However, no interaction between hemisphere, condition and participant was present ($F(1, 36) = .372$, $p =.546$). Further ANOVA's were conducted for the LIFG and RIFG separately to examine these significant effects.

6.3.5 LIFG D-HB. A two-way mixed ANOVA was used to assess the effect of the conversation condition on D-Hb within the LIFG between PWS and TS. There was a significant main effect of conversation condition ($F(1, 36) = 141.432$, $p<.001$), indicating LIFG activity was significantly was greater in the Social Conversation condition (mean: .091, SD: .242) compared to the Audio Conversation (mean: -.590, SD: .246) condition.

There was also a marginally significant interaction between conversation condition and participant group ($F(1, 36) = 3.987$, $p = .053$), indicating PWS and TS displayed differing levels of LIFG activity across Social and Audio Conversation conditions. These significant effects were followed up with independent samples t-tests.

The independent samples t-tests compared levels of D-Hb between PWS and TS across audio and conversation speaking conditions for the LIFG. PWS and TS showed similar levels of D-HB in the Audio Conversation condition, as seen in Table 30 and plotted in Figure 24, hence there was no significant difference within this condition, $t (36) =-.339$, $p = .736$. This contrasted with what happened in the social conversation condition, where PWS (mean: .185, SD: .203) showed significantly greater D-Hb, and thus LIFG activity, compared to TS (mean: -.020, SD: .254) indicating greater LIFG activity; $t (38) =2.834$, $p = .007$.

Table 30.

Mean (SD) LIFG D-Hb levels for PWS and TS across Audio and Social Conversation conditions

	Audio Conversation	Social Conversation
PWS	-.603 (.281)	.185 (.203)
TS	-.575 (.208)	-.020 (.254)

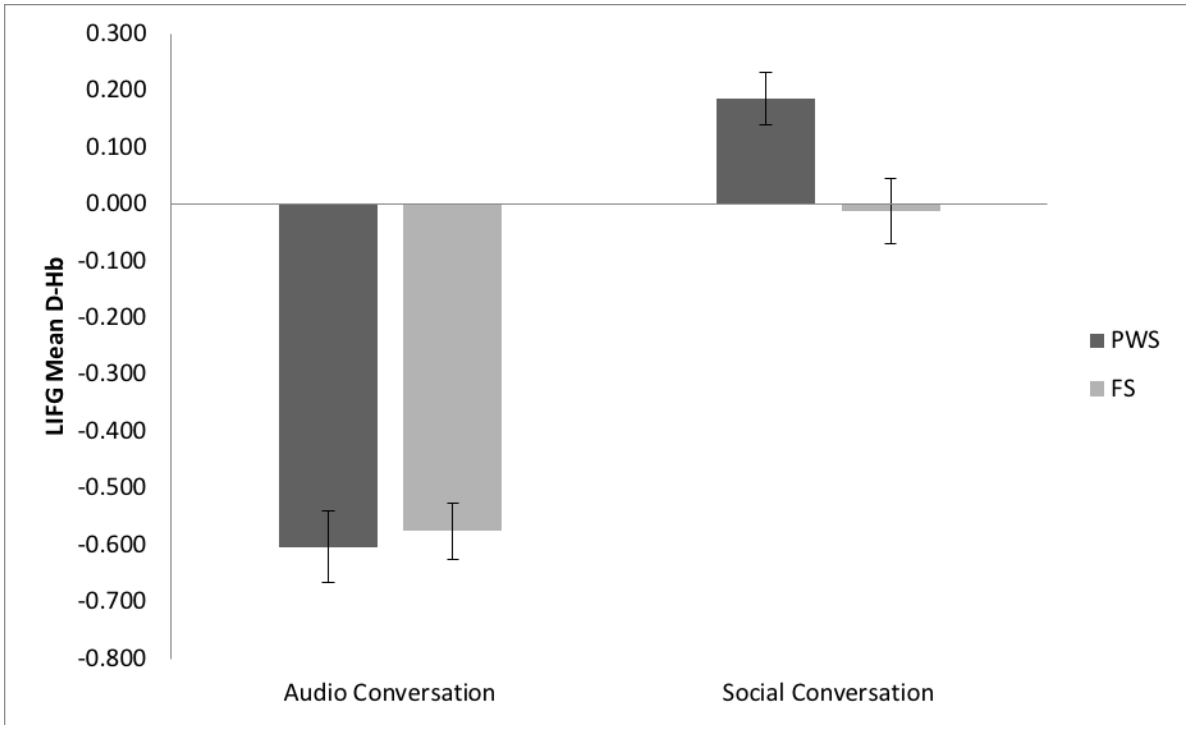

Figure 24. LIFG mean D-Hb levels across Audio Conversation and social conversation conditions for PWS and TS. Error bars indicate +/- one standard error.

6.3.6 RIFG D-HB. A two-way mixed ANOVA was also used to assess the effect of the conversation condition on neural activity within the RIFG between PWS and TS. Results showed a significant main effect of conversation condition ($F(1, 36) = 20.667$, $p<.001$), indicating RIFG activity in the Social Conversation condition (mean: .065, SD: .298) was greater than in the Audio Conversation condition (mean: -.205, SD: .285).

There was also a significant interaction between conversation condition and participant group ($F(1, 36) = 7.718$, $p = .009$), indicating differing RIFG activity between PWS and TS across Social and Audio Conversation conditions. The significant effects observed were followed up with t-tests.

Independent samples t-tests compared levels of D-Hb between PWS and TS across audio and conversation speaking conditions for the RIFG (Table 31 and Figure 25). TS showed greater D-Hb compared to PWS in the Audio Conversation condition, but this difference was not significant, $t (36) =-1.512$, $p = .139$. PWS in contrast displayed greater D-

Hb compared to TS in the social conversation condition, but this difference also was not significant, t (38) =1.549, p = .130.

Table 31.

Mean (SD) RIFG D-Hb levels for PWS and TS across Audio and Social Conversation conditions

	Audio Conversation	Social Conversation
PWS	.271 (.277)	.153 (.295)
TS	.133 (.284)	.005 (.306)

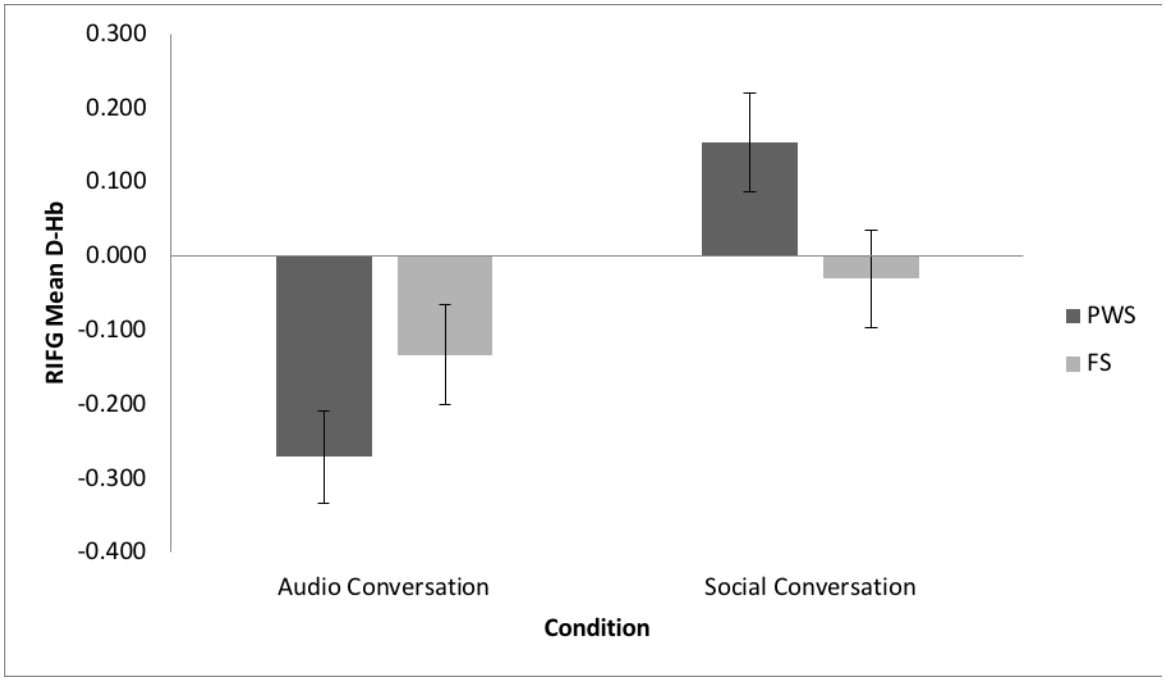

Figure 25. RIFG mean D-Hb levels across Audio Conversation and social conversation conditions for PWS and TS. Error bars indicate +/- one standard error.

6.3.7 Summary. Overall, results showed that the social conversation condition significantly and uniquely engaged the LIFG, indicated by greater D-Hb, compared to the Audio Conversation condition within PWS and the social conversation condition in TS.

6.4 Discussion

6.4.1 Overall findings. In this study, fNIRS was used to explore the neural basis of speech production in PWS and TS during a face-to-face conversational task. Participants responded to conversational questions whilst either face to face with a researcher, or whilst in the testing room alone in response to pre-recorded audio questions. We hypothesised PWS would display significantly different speech production neural activity (D-Hb) in the LIFG and RIFG compared to TS in both the Audio Conversation and Social Conversation conditions. Overall, results showed that PWS had significantly greater neural activity, indicated by greater D-Hb, within the LIFG compared to TS in the Social Conversation condition. Neural activity was similar between TS and PWS in the Audio Conversation condition and as such no significant differences were present for the LIFG and RIFG. Furthermore, RIFG over-activation was observed compared to TS in the Social Conversation condition, but this difference was not significant.

6.4.2 Increased RIFG activity in PWS compared to TS. Our results for the RIFG, although not significant, are consistent with previous research in PWS showing an over activation of the RIFG during speaking in PWS compared to TS (Belyk et al., 2015; Brown et al., 2005; De Nil et al., 2008; Lu et al., 2009; Neef et al., 2016; Neumann et al., 2005; Watkins et al., 2008). Such over activation of the RIFG in PWS is thought to reflect compensation for the structurally and functionally deficient LIFG (Chang et al., 2008; Kell et al., 2009; Lu et al., 2009; Sommer et al., 2002; Sowman et al., 2014; Watkins et al., 2008). Some studies suggest increased RIFG activity is linked to reduced stuttering (Braun et al., 1997; Kell et al., 2009; Preibisch et al., 2003). Within our study however, levels of stuttering were high despite this increased RIFG activity. It is possible that the RIFG was still attempting to compensate for the deficiencies of the LIFG, which although engaged in the task, is still structurally impaired in PWS. In addition, the increased RIFG activity in PWS observed in our study may reflect decreased automaticity and increased effort to speak with a fragile motor system which is taxed during speaking (De Nil et al., 2008).

6.4.3 Increased LIFG activity in PWS compared to TS. PWS displayed increased LIFG activation within the Social Conversation condition compared to the Audio Conversation condition. This pattern of activity was different to previous literature, which typically shows reduced LIFG activity during speaking in PWS compared to TS (Civier et al., 2017, Neef et al., 2018). A possible explanation for the observed differences between Audio and Social Conversation conditions could be because of practice in the Audio Conversation condition. However, this is unlikely as the practice condition contained 3 trials, and the voice of the interlocutor during the practice recordings was not the same as the voice of the interlocutor during the experimental session of the Audio Conversation condition. Overall, the pattern of activity observed in our study across conditions indicates a unique role for the LIFG in the Social Conversation condition. As both the Social Conversation and Audio Conversation condition involved speaking using long utterances (20 seconds) of connected speech, and there were no significant differences in stuttering severity across conditions, this unique pattern of activity is likely to reflect processes beyond speech production mechanisms.

6.4.4 Increased LIFG activity may not be associated with stuttering. Our results seemingly suggest that the mechanisms of stuttering in PWS operate beyond the LIFG in PWS during face-to-face conversation. PWS displayed similarly high levels of stuttering between Audio Conversation (8.91%) and Social Conversation (11.02%) conditions. Despite no significant difference in overt stuttering severity between conditions, patterns of LIFG neural activity were markedly different during these conditions. PWS displayed similar levels of LIFG deactivation to TS during Audio Conversation yet displayed significantly increased LIFG activation compared to TS during Social Conversation. Whilst the LIFG is structurally and functionally abnormal in PWS compared to TS (Brown et al., 2005; Etchell et al., 2018; Watkins et al., 2008), it is probably part of a wider network of regions in which dysfunction results in stuttering (Etchell et al., 2018; Neef et al., 2018). For example, research suggests stuttered speech is related to increased bilateral SMA activation and reduced bilateral

primary auditory cortex activation in PWS compared to TS; whereas fluent speech production is linked to increased right pre-SMA and reduced left auditory cortex activity (Belyk et al., 2014; Budde et al., 2014). Stuttering is therefore the result of network level, rather than single region, impairments across the speech motor network.

6.4.5 Increased LIFG activity may reflect task complexity, social evaluative processes and attentional demands. Our results are not consistent with Toyomura et al. (2018) who observed reduced LIFG activity in a study involving face-to-face conversation via a video link in an MRI scanner. Although our studies were similar, there are some fundamental differences that make comparison difficult. The stimuli used by Toyomura et al. (2018) were simple questions with simple "automatic" answers e.g. "Please tell me your postal number". In contrast, our study involved 20-second utterances of natural connected speech around an open-ended question (e.g. "What are you looking forward to this week?"). Hence, the complexity of the utterances made by our participants was greater than those in Toyomura et al. (2018). In addition, although the task in Toyomura et al. (2018) task involved face-to-face interaction, it was conducted via video link inside an MRI scanner. This in turn may have reduced the influence of social evaluative processes that are part of face-to-face interactions. Overall, the influence of stimuli complexity and social evaluative processes emerge as two explanations for the significantly increased LIFG activity observed in the Social Conversation condition between PWS and TS in our study. Perhaps both are subserved by the LIFG.

The pattern of LIFG neural activity observed in our study may be a reflection of the high complexity of the task in our study. Research consistently shows that increased speech stimuli complexity (e.g. from monosyllabic to trisyllabic) leads to greater activation of the LIFG (Blank et al., 2002; Horwitz et al., 2003; Moser et al., 2009; Sörös et al., 2006; Wise et al., 1999). This increased activity during speech tasks is probably due to increased demand on phonological processing and speech motor planning. In contrast, tasks involving naming highly familiar pictures, repetition of simple phrases and single words do not show high

engagement of the LIFG (Etard et al., 2000; Murphy et al., 1997; Sörös et al., 2003; Wise et al., 1999). Therefore, it is consistent with previous research that a connected naturalistic speech task containing long utterances as in our study would result in increased LIFG activity. In support of this this idea, Lu et al. (2010) showed that when naming pictures of 5-7 syllables in length compared to 3 syllables, TS showed significantly greater LIFG compared than did PWS. However, there was no difference in LIFG activity between short and long picture naming in PWS. The authors claimed that this was evidence for reduction in the function of this area during speech motor control in PWS. Complexity of the stimuli and our task may therefore not be a complete explanation for the pattern of results observed in our study.

An alternative explanation for the increased LIFG activity in the Social Conversation condition is that this pattern of activity reflects social evaluative processes rather than speech motor processes. Research suggests the LIFG is part of the social brain network that is associated with social evaluative processing, e.g. reading emotions, during social situations such as face-to-face conversation (Blakemore, 2008; Cavallo et al., 2015; Dal Monte et al. 2014). Hence, an increase in LIFG activity during a face-to-face interaction may reflect social evaluative processing. This is a plausible explanation for the increased LIFG activity observed in the Social Conversation condition as PWS display significant levels of social anxiety, which is associated with increased social evaluative processing (Iverach et al., 2017).

In support of this idea, Fales et al. (2010) showed increased anxiety levels led to increased LIFG activity in response to fearful, compared to neutral, targets. Weaker LIFG activation was observed in response to happy, compared to neutral, targets. This finding is consistent with findings from other studies that show increased LIFG activity in patients with social anxiety during social tasks such as affective processing (Heitmann et al., 2017) and affective Go/No-Go (Brown et al., 2015). Anxiety has therefore been shown to directly affect LIFG activity. However, Toyomura et al. (2018) found decreased LIFG activity during their face-to-face task with PWS. This finding occurred despite participants having higher anxiety

ratings in the face-to-face condition compared to the control condition, and this anxiety being linked to increased stuttering as well as increased amygdala activity. The authors attributed this difference to PWS being unable to devote sufficient attention to the face-to-face condition, having to dedicate their attentional resources to struggling to produce speech. Such an account may provide an explanation for our findings in that due to the interpersonal nature of our task, PWS could not avoid devoting attentional resources to the face-to-face condition. Hence, the increased LIFG activity observed within our Social Conversation condition may indeed reflect social evaluative processes (Fales et al., 2010).

A further possibility is that alongside task complexity and social evaluative processes, our results may be a reflection of attentional and cognitive processing impairment in PWS. During the experiment, participants were required to maintain eye contact with the interlocutor. Research has demonstrated PWS often have difficulty maintaining eye contact, which is thought to be a safety behaviour characteristic of social phobia and social anxiety (Lowe et al., 2012). However, it may be the case that eye contact, simultaneous with speech production, places excessive demand on attentional resources in PWS.

Loss of eye contact has been suggested to be an automatic mechanism by which an individual disengages from the environment and diverts attentional resources towards enhancing cognitive processing (Glenberg, Schroeder & Robertson, 1998; Smallwood & Schooler, 2006). For example, Annerer-Walcher, Körner and Benedek (2018) used eye tracking to demonstrate participants disengage and decouple from the environment when turning attention inward to calculate mathematical problems. In addition, Kajimura and Nomura (2016) demonstrated that eye-contact impaired performance on a verb generation task, compared to an averted eyes condition. Crucially, this impairment of performance was only present when task demands were high. The authors consequently suggested that loss of eye-contact during high task demands occurred to enable engagement of a “general cognitive system”, which supported the verbal system when completing the verb generation task. Eye-contact was therefore suggested to share domain-general cognitive resources with

speech preparation and production systems. Such research therefore suggests that eye contact during a speech task may not only lead to detrimental performance but may encroach on the attentional resources needed for speech production. Hence, loss of eye contact in PWS may be an automatic response in an attempt to divert attention resources away from the environment and towards speech production which is excessively demanding. This is of importance to interpret our findings as research indeed shows PWS have impaired attentional capacity.

Research demonstrates PWS have significantly impaired performance, compared to TS, on dual-task paradigms where there is a distractor task to be completed alongside a main task (Smits-Bandstra & De Nil, 2008). Such findings illustrate PWS have reduced attentional and cognitive processing resources to devote to competing tasks. In addition, neuroimaging research has suggested that speech production is atypically resource demanding in PWS compared to FS. In a study by Maxfield et al. (2016), PWS and TS named pictures which were overlaid with distractor words, whilst monitoring low and high times which varied in frequency and onset. Cognitive processing resources were assessed by monitoring EEG P3 amplitude, which is a measure of availability of cognitive resources for completing target perception and categorization tasks (Luck, 1998). Results showed no difference in P3 amplitude when task demands were low. However, when dual task demands were high, PWS showed decreased P3 in comparison to TS. These findings therefore suggested that PWS had decreased cognitive and attentional processing resources available when completing a high demand task.

Taking previous literature into account, it could be argued that the Social Conversation condition in our experiment acted similarly to a dual-task paradigm. PWS were required to produce spontaneous speech, as well as maintain eye contact with an interlocutor throughout the experiment. Therefore, it is possible that the IFG was not only engaged in speech production, but also in social processing of the interlocutor, as the LIFG is part of social brain network associated with social evaluative processing (Blakemore, 2008; Cavallo et al., 2015; Dal Monte et al. 2014). Heightened LIFG activity in the Social

Conversation condition may therefore reflect the attentional and cognitive processing demand on the LIFG, being involved in complex speech production alongside social evaluative processing via two overlapping networks.

In summary, the significantly increased LIFG activity observed in PWS, compared to TS, in the Social Conversation condition may be a reflection of speech utterance and production complexity, social evaluative processes and attentional and cognitive processing demands.

6.4.6 Increased LIFG activity may facilitate tDCS effects in face-to-face conversation. The Increased LIFG activation during face-to-face conversations observed in our study may indicate how to facilitate tDCS effects. As tDCS requires engagement of a targeted region for the enhancement of excitability (Woods et al., 2016), it is possible that tDCS interacted with boosted LIFG activity during face-to-face conversation to provide speech motor facilitation that resulted in reduced stuttering in our study in Chapter 5 and Chesters et al. (2018). As levels of stuttering were similar across conditions in our experiment, stuttering reduction as a result of LIFG tDCS is likely to be a result of enhancement in regions interconnected to the LIFG within the speech motor network. A possible mechanism of such an effect is the enhancement of communication between the LIFG and sensorimotor integration regions such as the orofacial primary motor cortex, which shows impaired excitability in PWS compared to TS (Neef et al., 2015). The application of tDCS to the LIFG therefore may result in spreading tDCS current via interconnected tracts to regions supporting fluent speech motor production and leads to stabilised and enhanced sensorimotor plan activation in PWS (Chesters et al., 2018).

6.4.7 Limitations and future work. This study has several limitations and presents many opportunities for future work. One limitation of this study is that factors such as vocal pitch, vocal tone and facial expressions of the interlocutor were not controlled. Research shows such factors convey positive or negative feedback to the speaker, from the listener,

during speech (Leongomez, Mileva, Little & Roberts, 2017). Consequently, such feedback may affect a speaker's anxiety, fluency levels and neural activity related to speech production and social evaluative processes. The use of virtual reality (VR) in future work would allow for high levels of control for listener characteristics in studies involving face-to-face interaction (Vanryckeghem et al., 2017). Research has shown interactions with virtual humans in VR environments can feel as real as interactions with non-virtual humans (Morina, Brinkman, Hartanto, Kampmann & Emmelkamp, 2015). Hence, VR may be a useful adjunct to face-to-face interaction studies in future work to overcome limitations related to the effect of listener characteristics and perceived social evaluation on a speaker.

In addition, Toyomura et al. (2018) showed anxiety and associated amygdala activity significantly correlated with incidence of stuttered speech, illustrating anxiety directly influences levels of stuttering. It is therefore a further limitation that our current study did not assess self-reported anxiety levels during the task itself. Such data would be useful to collect in future work to assess the effect of anxiety on speech motor processes across conditions. Such work could be combined with VR paradigms to modulate sources of social stress (e.g. negative facial responses) within the virtual testing environment to assess their effect on speech production mechanisms. In addition, our study could be replicated in TS with social anxiety in order to validate the idea that patterns of LIFG activity observed in our study are associated with social evaluative processes.

A further limitation of our study is that the complexity of the stimuli used in our study was not controlled. Although a connected speech task is more complex than single word production, variations in stimulus complexity were not used to further assess the potential interaction between stimuli complexity and speech production neural activity. One such way to adjust task complexity would be to implement a speaking task with varying levels of phonological complexity. Previous research has shown that stuttering is more likely to occur on words with high phonological complexity compared to low complexity (Dworzynski & Howell, 2004; Howell & Au-Yeung, 1995; Howell & Au-Yeung, 2007; Howell, Au-Yeung, Yaruss & Eldridge, 2006; Wolk & LaSalle, 2015). Speaking complexity could further be

modulated using different rates of production (Alexandrou et al., 2017) to vary the level of processing load and efficiency required within speech motor preparation and production systems. Hence, neural differences in PWS compared to TS when producing high complexity words under a face to face (arguably a high complexity condition) and audio condition (low complexity) could be assessed to provide insight into the interaction of these factors on stuttering mechanisms and neural activity.

The neuroimaging method used in this experiment, fNIRS, is also functionally limited to detection of neural activity no deeper than 1.5cm into the cortex (Quaresima & Ferrari, 2016). As a network of cortical and subcortical regions enables speech production (Price, 2012), capturing a whole brain view of speech within our conditions is necessary. To achieve this, multi-modal imaging techniques could be used. For example, EEG and fNIRS may be combined to obtain data within ecologically valid paradigms from both cortical and subcortical regions that have been implicated in stuttering such as the LIFG, basal ganglia and cerebellum (Alm, 2004; Giraud et al., 2008). This combination of neuroimaging methods is therefore particularly ideal for stuttering as it allows neuroimaging in naturalistic settings while capturing electrophysiological and haemodynamic neural activity across cortical and subcortical regions. This would allow for a deeper and fuller insight into the mechanisms of stuttering within ecologically valid paradigms and environments, compared to using one neuroimaging modality alone.

A further limitation within this experiment is that data for neural regions beyond the LIFG and RIFG were collected during our experiment, but not analysed, as they were not relevant to our hypotheses. Analysis of the data in our experiment relating to other neural regions would be useful for developing a more complete picture of the mechanisms of stuttering within the conditions of our experiment. In particular, analysis of other neural regions will allow an understanding into the patterns of activation and deactivation observed in our conditions, and how they relate to the wider speech motor network. It is of interest to assess STG and premotor cortex activation across conditions due to their links to stuttering severity (Garnett et al., 2018; Neef et al., 2016).

Future analysis could further attempt to examine neural data in relation to stuttering severity. Participants could be grouped into high and low fluency PWS according to their percentage of syllables stuttered during the task as in Toyomura et al. (2018). Future analysis of data from our experiment could also explore neural activity on an individual trial basis. For example, every individual trial across participants could be classified as high or low stuttering according to a percentage syllables stuttered threshold. Comparisons could then be made across high and low stuttering trials to gain insight into the mechanisms of high and low stuttering within face-to-face conversational settings. In addition, neural variability amongst PWS was demonstrated as 7 PWS displayed greater D-Hb levels in the Audio Conversation condition compared to the Social Conversation condition. Further analysis to explore this difference may provide insight and evidence into the existence of subtypes of PWS that have been recently demonstrated (Ajdacic-Gross et al., 2018). In addition, analysis based on observed symptoms of stuttering could be conducted. Research by Jiang et al. (2012) suggests stuttering symptoms such as repetitions, prolongations and blocks are associated with increased activity in the LIFG and precuneus. In contrast, phrase repetitions and pauses are associated with increased subcortical activity in the putamen, cerebellum and globus pallidus. Hence, neural activity patterns may be different across PWS depending on the stuttering symptoms they present. Such approaches to analysis could allow deeper insight into the mechanisms for fluent and stuttered speech for PWS within our conditions compared to traditional experiments. Consequently, neural regions that serve as targets for future brain stimulation studies seeking to reduce stuttering may be elucidated.

In addition to individual analyses, there are further ways in which neural data could be explored. This report considered neural activity during speech production. However, neural activity was also recorded prior to speech production, during a period of speech perception (listening to the interlocutor speak). In addition, neural data were also collected during a speech anticipation (Rest I) phase. Anecdotally, PWS can often predict stuttering, which can lead to avoidance of anticipated stuttered words (Bloodstein & Ratner, 2008) and induce speaking related anxiety (Jackson et al., 2015). Such anxiety is manifested in

increased pulse and vasoconstriction (Van Riper & Milisen, 1939), which consequently may affect neural activity levels observed with fNIRS in conversational paradigms. Hence, exploration of neural activity in PWS at different stages of our task may allow deeper insight into the mechanisms of stuttering across the conditions of our experiment.

6.4.8 Summary. Results demonstrated LIFG neural activity differed from that seen in TS and this region was critically engaged in PWS during a face-to-face social interaction task when speaking in the presence of another person. This study is the first to explore neural activity within face-to-face, ecologically valid, social interactions in PWS using naturalistic connected speech tasks. Results show the mechanisms of stuttering in PWS may differ within face-to-face social interactions compared to previous studies that have used simple and low complexity speech production paradigms. LIFG activation during face-to-face social interaction may not reflect dysfunctional speech production but rather social evaluative processes linked to anxiety experienced by PWS. Further work is required to validate this idea.

Our results underline the importance of understanding the mechanisms of stuttering across different contexts to provide a complete neural picture of stuttering. A more complete, ecologically valid, picture of the stuttering brain will further allow for the development of interventions for stuttering. Current therapies for stuttering are significantly limited due to therapeutic effects being difficult to transfer into real world settings (Baxter, 2015). Without an understanding of the mechanisms of stuttering in real world settings, brain stimulation interventions for stuttering are likely to face the same real-world transfer limitations of current therapies. Hence, further face-to-face interaction work with PWS is required to elucidate mechanisms of stuttering within ecologically valid settings, with ecologically valid stimuli, to elucidate neurostimulation targets to enable the development of effective interventions for stuttering.

Chapter 7 – General Discussion

The first studies in this thesis established whether or not tDCS applied to the LIFG affected speech production processes in TS and PWS. Stimulating the LIFG improved speech production in TS (Chapters 3 and 4). An important finding was that tDCS had clearer impact in improving the fluency of difficult material. The standard approach to using tDCS in interventions is to choose a conventional treatment that has a large effect and couple this with tDCS that (as a rule of thumb) roughly doubles the effect of the original treatment (Baker et al., 2010; Fridriksson, Richardson, Baker & Rorden, 2011; Marangolo et al., 2014). Based on the studies on TS, a fluency shaping therapy approach was chosen which requires PWS to perform various demanding activities and which has a large effect on stuttering (De Nil et al., 2003; Neumann et al., 2005). Fluency shaping therapy was coupled with tDCS to the LIFG and provided promising indications for the efficacy of this approach. Further participants are needed to provide sufficient statistical power to achieve significance (effects just reach trend significance at present with N=14 PWS). The fluency shaping therapy examined in Chapter 5 required PWS to work face to face with SLTs and the largest effects with the therapy were seen in aspects of the assessments that required this mode of communication. Whilst the work in earlier chapters had focused on the LIFG's role in speech production, it is also possible that it serves other functions such as responding in different ways in situations with different levels of anxiety (face to face communication is anecdotally reported to lead to high anxiety in PWS). Chapter Six used fNIRS as a technique to examine the response of the LIFG when communicating in different styles (face to face or audio alone). The results clearly indicated that the LIFG was involved differentially when PWS communicate in different styles. The implications for future research are that whilst other perspectives suggest stimulating the LIFG activates an extensive network extending to the cerebellum and basal ganglia, activity in frontal areas seems equally important particularly when investigating therapies that address anxiety as well as speech symptoms.

7.1 tDCS effects on speech production in TS

In Chapter 3, we used tDCS over the LIFG (2 mA anodal or sham tDCS for 20 minutes) to attempt to improve SRTs in a picture naming task in young adult TS (Study 1.1). Young TS participants were employed because the majority of studies which have used tDCS to improve speech production have involved older individuals. This is probably because stroke-related speech impairments occur predominantly in older individuals and not younger ones, and previous tDCS studies have been conducted to develop interventions for such individuals. As stuttering happens at any age, it was necessary to validate that tDCS improves speech production when applied to younger adults. The task in Study 1.1 involved a classic picture naming task, in which the level of speech preparation was manipulated using pictures that led to one or three-syllable names. Production of monosyllabic words requires low levels of speech preparation. Conversely, multi-syllable words are more complex, require increased speech preparation and involve increased engagement of the LIFG compared to monosyllabic words (Sörös et al., 2006). As tDCS effects are likely to depend on task demands and complexity, we hypothesised that anodal tDCS, over the LIFG would result in significantly reduced SRTs for both one and three syllable words compared to sham tDCS but that the effects would be greater for the three syllable words. We did not find a significant difference in SRTs in TS between anodal tDCS compared to sham tDCS for one syllable words. However, anodal tDCS resulted in a significant reduction of SRTs for three syllable words in our picture naming task compared to sham tDCS. We therefore demonstrated LIFG tDCS can enhance speech preparation processes. As we observed an effect of tDCS on three syllable words, but not one syllable words, it is likely that the effects observed were a result of an interaction between tDCS and the complexity of the stimuli.

In our second tDCS study (Study 1.2) we used the same stimulation paradigm (2 mA LIFG or sham tDCS for 20 minutes) as in Study 1.1. RIFG was a control site stimulated by anodal tDCS and was expected to have no effect. Similar to Study 1.1, we assessed the effect of tDCS on SRTs (and thus speech preparation) on a picture naming task with three syllable picture name stimuli. However, our picture naming task was modified from that used

in Study 1.1 to include primes prior to the picture stimulus that would allow for speech preparation (congruent primes i.e. the name of the upcoming image) or result in speech preparation for the wrong word, requiring reformulation of speech preparation (incongruent primes i.e. the primes did not match the upcoming picture). It was predicted that anodal tDCS would result in quicker SRTs compared to sham tDCS, and that this difference would be greater for incongruent trials. The results showed that LIFG anodal tDCS resulted in significantly faster SRTs compared to sham tDCS for incongruent words (complex stimuli requiring reformulation of speech preparation) but not congruent words (simple stimuli where speech preparation demands are low). No RIFG stimulation effects were observed. Results in this chapter therefore validated that complexity of stimuli is key to producing tDCS effects and modulation of speech preparation processes, as significant modulation of SRTs was observed only for complex stimuli after LIFG tDCS.

Results from Chapter 3 showed that anodal tDCS can enhance speech preparation in young TS, particularly for complex stimuli requiring increased levels of speech preparation that presumably resulted in increased engagement of the LIFG compared to simple stimuli. Consequently, in Chapter 4, we conducted a third tDCS study (2 mA LIFG or RIFG anodal, cathodal or sham tDCS for 20 minutes) with young TS to explore the effect of tDCS on VRTs for repetition and articulation of complex connected speech stimuli (i.e. tongue twisters). As in Study 1.2, the control stimulation was the RIFG which was stimulated in a second group of participants to assess the specificity of any LIFG tDCS effects. In addition, cathodal tDCS, which is thought to inhibit stimulated regions, was also employed in this study to further assess the effect of tDCS on speech preparation. Tongue twister repetition VRTs (time to produce the entire tongue twister) were assessed one hour before, during and one hour after the end of the tDCS stimulation session. We hypothesised that anodal tDCS would result in significantly quicker tongue twister repetition VRTs in the session where tDCS was applied, compared to sham tDCS. In addition, we hypothesised that cathodal tDCS, would result in a significant increase in tongue twister VRTs during stimulation compared to sham tDCS because this stimulation should inhibit the LIFG and result impede speech preparation. No

other significant differences were expected across time points or stimulation types. In particular, no effects of RIFG (the control site) stimulation were expected. The results showed that anodal tDCS resulted in significantly quicker tongue twister VRTs compared to sham and cathodal tDCS during stimulation. No other significant effects on tongue twister VRTs were observed for LIFG or RIFG stimulation across other stimulation types and time points. Therefore, the results from this and the previous studies demonstrated LIFG anodal tDCS leads to enhanced speech preparation and articulation in TS.

In summary, our results from tDCS studies with young TS in Chapters 3 and 4 showed that anodal LIFG tDCS can significantly enhance speech preparation. These effects were predominantly observed on stimuli which required high levels of speech preparation and complexity i.e. three syllable words and tongue twister stimuli. Our findings are consistent with reports demonstrating that the LIFG is crucially involved in speech preparation, particularly research showing disruption of the LIFG results in slowed speech timing and slowing of vocalisations (Long et al., 2016). Consistent with such findings, enhancement of the LIFG using anodal tDCS resulted in quicker speech timing and quicker SRTs and VRTs compared to sham tDCS. Our tDCS studies with TS therefore provided the proof of principle that LIFG tDCS (2 mA, 20 minutes) can be used to enhance speech preparation processes, particularly when task demands and complexity are high. Consequently, we attempted to reduce stuttering in PWS by applying tDCS alongside a challenging intervention which aimed to increase speech fluency.

7.2 tDCS effects on speech production in PWS

In Chapter 5, we attempted to use tDCS to reduce stuttering in PWS by applying LIFG tDCS alongside a challenging fluency shaping therapy to enhance the effects of the intervention. The LIFG is structurally and functionally impaired in PWS compared to TS and these impairments are thought to contribute to stuttering severity. Recovery from stuttering and increased fluency is linked to increased activity in the LIFG in PWS. In addition, as previous research and our studies in Chapters 3 and 4 that showed, task complexity is key

for induction of positive tDCS effects. Therefore, we delivered tDCS over multiple sessions concurrent with a clinical stuttering intervention (fluency shaping). The intervention chosen was known to be challenging but efficacious and could induce significant reductions in stuttering and result in normalisation of LIFG functional activity. A total of 14 PWS participated, of whom 7 received anodal tDCS and 7 received sham tDCS over the LIFG (20 minutes) concurrent with the fluency shaping intervention. It was found that tDCS resulted in reductions of percentage syllables stuttered during conversation, which were trending towards significance. Despite the small sample size and variability of stuttering, this study showed tDCS is a promising adjunct to therapeutic interventions to reduce stuttering in PWS.

7.3 Neural activity in the LIFG during face to face speaking

In Chapter 6, we explored the neural basis of speech production in PWS and TS using fNIRS in a conversation style task. This was due to tDCS showing the greatest effect in reducing stuttering during the ecologically valid conversation assessments in Chapter 5. In addition, LIFG neural activity in PWS had not been examined previously in experiments with ecologically valid stimuli (i.e. conversation). Such research is important to understand the mechanisms of speech breakdown within real world contexts. These mechanisms could then be targeted with an intervention which would likely enable transfer and generalisability of treatment effects from clinical settings to the real world. Furthermore, such research is necessary to understand the role of the LIFG in processes beyond speech production e.g. anxiety.

Two conditions were used: Social Conversation (face to face dialogue with a researcher) and Audio Conversation (speaking in turn with pre-recorded audio with no researcher present). Neural activity within the RIFG was also assessed due to its role in compensation for stuttering. The results showed that PWS had significantly greater neural activity in the LIFG compared to TS in the Social Conversation condition. LIFG activity in the Social Conversation condition was interpreted as due to processes beyond speech

production (e.g. social evaluative processes), as levels of stuttering in the Audio and Social conditions were similar. The results demonstrated that the LIFG was differentially engaged for PWS depending on speaking style, with neural activity showing two distinct patterns: deactivation during Audio Conversation (similar to TS) and significantly increased activation (compared to TS) during Social Conversation. Levels of stuttering were not significantly different in PWS across conditions, possibly suggesting that the patterns of LIFG activity observed reflect a response to situational factors such as anxiety.

7.4 Limitations and Future Work

7.4.1 Use of neuroimaging is crucial for neurostimulation studies. A fundamental limitation of the tDCS work presented in this thesis is that neuroimaging was not used to assess tDCS effects with TS and PWS. The putative effect of tDCS on brain mechanisms is therefore circumstantial and not conclusive, as no evidence of mechanism was obtained using neuroimaging. Our studies therefore lack the mechanistic insight into the tDCS-induced enhancement of speech production in TS and PWS we observed in our studies.

Research has demonstrated that tDCS effects may not be limited to the targeted region as the brain is a complex hierarchical system with multiple anatomically and/or functionally interconnected systems and subsystems (Engel et al., 2001; Roux & Buzsáki, 2014). Therefore, perturbing one region of a system will most probably also affect other, functionally connected areas. Stimulating the primary motor cortex, for example, can influence the activity of the supplementary motor area or of even remotely connected subcortical regions (Antal et al., 2011; Polanía, Paulus, & Nitsche, 2012). Furthermore, the spread and effectiveness of tDCS current may differ across TS and impaired populations due to differences in neural structure and excitability (Lefebvre & Liew, 2017). Hence, modulation of behaviour as a result of tDCS may result from the effect of tDCS on wide and distributed neural network. For example, the effects observed in Chesters et al. (2018) and

in our study might have resulted from enhancement of the LIFG itself and thus quicker speech preparation, or enhancement of transfer of speech preparation plans to the orofacial motor cortex for execution (Neef et al., 2015), or enhancement of the basal ganglia through LIFG interconnections resulting in increased efficiency of rhythm and sequencing of speech (Giraud et al., 2008), or enhanced connectivity and transfer of information around the whole BGTC loop necessary for speech preparation and production (Bareš et al., 2007; Bender et al., 2004). Neuroimaging is therefore essential for understanding the mechanisms and effect of tDCS, and how they may differ, in both TS and PWS in order to optimise stimulation protocols and mechanistic understanding of speech production for future studies.

The use of neuroimaging in tDCS studies is further considered to be one of a number of best practices for conducting high quality tDCS studies (Woods et al., 2016). Future tDCS studies in stuttering have the advantage of being able to use the extensive tDCS knowledge-base that exists about neurostimulation best practice. Current opinion suggests that for the highest quality outcomes, studies should: employ neuro-navigation to ensure accuracy and homogeneity of electrode placement; include behavioural and control tasks to assess the effect of stimulation on function; stimulate control regions to test the functional specificity of the stimulation target region; combine stimulation with imaging to assess the effect of stimulation and targeted, neighbouring and distant cortical regions; and interpret stimulation-induced changes within theory-driven models which employ both behavioural and neural mechanisms (Polanía, Nitsche & Ruff, 2018). Such studies are crucial for providing evidence of cause and effect of a stimulation protocol. Findings from such high-quality studies could be used to make reliable and evidence based informed research choices regarding the development of adjunctive stimulation-based intervention paradigms for stuttering. The resources for conducting such studies were not available in our lab at the beginning of my PhD research. Hence, the exclusion of neuroimaging in our studies is down to accessibility rather than oversight. Such resources are now available (fNIRS and EEG) and all future neurostimulation work will use neuroimaging for the purposes described above.

7.4.2 Limited knowledge of the mechanisms of stuttering. As the research outlined in Chapter 2 showed, neural differences between PWS and TS are vast and there is no agreement as to how these differences result in stuttering (Etchell et al., 2018). Adding to this lack of agreement amongst studies within the field, our findings of increased LIFG activity during conversation in PWS in Chapter 6 showed a pattern opposite to that observed in PWS when speaking in fMRI studies which is possibly attributable to constraints when working with MRI in conversation tasks. Previous research has further shown variability of neural activity in PWS. Thus, Wymbs et al. (2013) reported a study where four male PWS covertly and overtly produced single words across two event-related fMRI sessions separated by at least three weeks. No common regions of activation were found across the four PWS in this study. There was some agreement in common neural activations present between participants 2 and 4 for the left precentral gyrus, right anterior insula, left cerebellum lobule IV; and participants 3 and 4 for the right supplementary motor area and right precentral gyrus. However, the within subject neural activity across sessions was high. Such research indicates there are likely to be individual differences in functional neural activity patterns in PWS, but these differences may be stable and consistent within an individual over time. These patterns of neural activity may further be different across situations as observed in Chapter 6. Here we observed deactivation of the LIFG, on a level similar to TS during Audio Conversation but increased LIFG activity compared to TS during Social Conversation. Such differences in neural activity potentially allude to task-related and individual differences in PWS neural activity across situations and contexts.

In real-world settings, the level of stuttering produced by PWS varies across situations such as speaking on the phone (increased stuttering; Palasik, Irani & Goberman, 2009) and day to day, as well as within situations on the same day (Arenas, 2017; Constantino, Leslie, Quesal & Yaruss, 2016; Iverach et al., 2011). This variation in severity can be as large as 25% syllables stuttered (Constantino et al., 2016). Evidence of this variability in stuttering largely comes from self-report studies and few investigations to date have examined variability of stuttering in experimental settings or with neuroimaging.

Neuroimaging investigations of such phenomena would allow insight into the neural mechanisms of speech in social situations, which can be modulated by anxiety and social factors.

For example, a study by Leongómez, Mileva, Little and Roberts (2017) found that perceived social status differences between a speaker and listener affects the speaker's vocal characteristics. In simulated job interviews with dominant, prestigious or neutral employers, participants, particularly those who perceived themselves as less dominant, increased their vocal fundamental frequency. Hence, people adjust their vocal parameters according to their perceived status in relation to another and the situational anxiety they feel. It is not understood how such parameters may manifest in PWS or affect levels of stuttering. Hence, it would be worthwhile in future studies, and perhaps in a re-analysis of our Chapter 6 data, to examine the vocal characteristics of PWS in relation to anxiety in face-to-face interactions.

Overall, there is a fundamental gap in our understanding of the real-world neural mechanisms of stuttering, which our findings allude to in Chapter 6. In addition, there is a lack of research and understanding around vocal characteristics in relation to anxiety, and how they may manifest in differential neural activity between high and low anxiety individuals and particularly PWS. Understanding the mechanisms of contextual variability of stuttering in ecologically valid settings is of particular importance for developing complete mechanistic frameworks of neural dysfunction associated with stuttering. Such research would allow us to formulate links between vocal factors, anxiety, neural activity and stuttering in PWS in real world situations. Findings from these studies will likely lead to the development of a rich and detailed picture of stuttering, which may provide the missing insights necessary for the development of long-term interventions and stuttering reduction through elucidation of targets for NIBS studies.

Crucially, the effects of NIBS and tDCS in particular rely on interaction and engagement with ongoing task-related neural activity (Stagg et al., 2011). If such task-related neural activity varies across individuals or across contexts (i.e. conversation vs.

picture naming), a tDCS protocol which reduces stuttering for one PWS may not produce an optimal effect in another PWS. An understanding of the mechanisms of stuttering within ecologically valid settings is therefore essential for the development of effective interventions. As interventions could be built upon a mechanistic framework of real-world stuttering and associated fluency, such interventions may be more resistant to relapse. Hence, NIBS interventions devised from real-world neuroimaging data in PWS would perhaps aid generalisation and transfer of positive intervention effects to real world settings, which current stuttering treatments largely fail to do (Baxter et al., 2016).

As a network of cortical and subcortical regions enables speech production (Price, 2012), capturing a whole brain view of speech production in such ecologically valid situations is necessary. To achieve this, multi-modal imaging techniques could be utilised. Retaining use of fNIRS in future studies is vital due to the advantages it presents for measuring cortical haemodynamic activity in ecologically valid paradigms. EEG is one method which is well suited for combination with fNIRS to assess neural activity in ecologically valid paradigms due to its non-invasive nature and high temporal resolution (Gevins, Leong, Smith, Le & Du, 1995). This combination of neuroimaging and physiological methods is particularly ideal for stuttering as it allows neuroimaging in naturalistic settings whilst capturing electrophysiological and haemodynamic neural activity across cortical and subcortical regions. For further exploration, physiological measures such as heart rate and galvanic skin-response (GSR) could be used to detect states of anxiety and their link to neural activity observed in PWS in face-to-face situations. Such multi-modal methods would significantly enhance our understanding of stuttering and the mechanisms of tDCS effects in both TS and PWS (Etchell et al., 2018; Woods et al., 2016).

7.4.3 Lack of oscillatory research with PWS. Understanding neural oscillatory in PWS is crucial as such data provides temporally sensitive reliable signatures associated with cognitive processes and behavioural states which have a role in the orchestration of brain functions and dysfunction (Reato, Rahman, Bikson & Parra, 2013; Schilberg et al.,

2018). Oscillatory research within PWS would allow insight into the mechanisms of stuttering, and perhaps its relation to anxiety, within real world and face-to-face settings. This is due to the high temporal resolution of oscillatory neuroimaging methods, enabling insight into the temporal aspects of the breakdown of fluent speech production.

There is a distinct lack of oscillatory research using EEG and stuttering. This is probably due to the sensitivity of EEG, where signals are easily contaminated due to movement of the head and jaw (Vos et al., 2010). Furthermore, such oscillatory studies are often excluded from meta-analyses in stuttering, due to the difficulty in aligning oscillatory results with haemodynamic imaging methods such as fMRI (Etchell et al., 2018).

Studies which have explored oscillatory aspects of stuttering have evidenced neural abnormalities during speech preparation and production stages. Prior to the production of stuttered words within PWS, compared to the production of fluent words, CNV slope is significantly lower, and this reduction correlates with stuttering severity and frequency (Vanhoutte et al., 2016). A CNV is a slow, negative event-related potential thought to reflect motor preparation generated by the BGTC loop (Bareš et al., 2007; Bender et al., 2004). Increased speech motor preparation enables fluent word production, and this speech motor preparation process is inefficient in PWS. Similarly, Mersov, Jobst, Cheyne and De Nil (2016) demonstrated that compared to controls, PWS showed stronger beta (15–25 Hz) suppression in the speech preparation stage, followed by stronger beta synchronization in the bilateral mouth motor cortex. PWS also recruited the right mouth motor cortex significantly earlier in the speech preparation stage compared to controls. The authors proposed that exaggerated beta synchronization indicates a strongly inhibited motor system that requires a stronger beta suppression to disengage prior to speech initiation. Additionally, Sengupta et al (2017) identified various anomalies in PWS, compared to TS, in EEG spectral power across alpha, beta and gamma bands, and anomalies in phase-coherence in the gamma band, preceding the production of stuttered utterances in PWS. Other oscillatory studies have shown a smaller negative slow wave indexing over auditory regions, postulated to demonstrate dysregulation of motor efference copy which is thought to

be responsible for conveying movement information to sensory areas before and during vocalisation (Mock, Foundas & Golob, 2015). Overall, biomarkers which can identify stuttering oscillatory activity seemingly exist, but require validation and replication.

Studies have also examined oscillatory activity within anxious individuals to determine oscillatory biomarkers of anxiety. Harrewijn, Van der Molen and Westenberg (2016) conducted an experiment where high and low socially anxious females watched and evaluated of a video of a speech by a peer, then prepared their own speech, which they believed would be recorded and evaluated by the peer. It was found that high socially anxious participants displayed significant negative delta–beta correlation compared to low socially anxious participants. It was proposed by the authors that this negative delta–beta correlation was indicative of increased activity in subcortical brain regions and decreased activity in cortical brain regions. Interestingly, no delta-beta correlation differences were found during rest, indicating a specific threshold of stress may be required to elicit negative delta-beta correlation in anxious individuals. In addition, Tarrant, Viczko and Cope (2018) found change of proportional power from high beta frequencies to low beta frequencies, particularly in the anterior cingulate cortex, after a VR social anxiety intervention. Hence, change in beta frequencies may be a biomarker for anxiety reduction post-intervention.

EEG research therefore indicates biomarkers for social anxiety related stress and recovery exist, as well as for the onset of a stuttering response. These biomarkers could be used together in future studies for further understanding of stuttering, its link to anxiety, and the development of interventions potentially tailored to different levels of anxiety within PWS. However, to date, no studies have measured oscillatory activity pre and post intervention or oscillatory activity associated with persistence and recovery (spontaneous or as a result of intervention) from stuttering. In addition, no studies to date have used EEG to measure anxious states during speaking in PWS. Once abnormal oscillatory profiles are reliably identified, as well as oscillatory profiles and changes associated with treatment and recovery, such oscillations can be targeted with neurostimulation techniques with a view to

developing clinical interventions. Oscillatory neural activity can be modulated using transcranial alternating current stimulation (tACS).

TACS involves application of sinusoidal currents via scalp electrodes to modulate neural oscillations and cortical excitability and synchronise neural activity underlying cognition and the temporal coordination of neural processes (Frohlich, 2017; Schilberg et al., 2018; Vosskuhl, Strüber & Herrmann, 2018). This is thought to occur by increasing the power of the oscillations or the phase-locking index between the driving and the endogenous oscillations (Helfrich et al., 2014; Neuling, Rach, & Herrmann, 2013). Importantly, tACS has been shown to be capable of modulating behavioural functions such as memory, attention and perception (Antal & Paulus, 2013; Fröhlich et al., 2015).

7.4.4 Individualised stimulation paradigms. Whilst neurostimulation methods such as tDCS and tACS are promising tools for intervention, fundamental limitations of neurostimulation remain such as: poor specificity and state-dependency of effects, variable effect sizes, variable effects across individuals, and limited knowledge of the neural mechanisms of neural stimulation (Fritsch et al., 2010; Guerra et al., 2017; Klaus & Schutter, 2018; Learmonth, Thut, Benwell & Harvey, 2015; Lefebvre & Liew, 2017; Li, Uehara, & Hanakawa, 2015; London & Slagter, 2015; Martin, Meinzer, Lindenberg & Sieg, 2017; Polanía et al., 2012; Westwood & Romani, 2017; Wiethoff et al., 2014; Zimerman et al., 2013). These factors, combined with the heterogeneity of stuttering (Wingate, 2002), individual variability of stuttering (e.g. Constantino et al., 2016), variability of stuttering neural activity (Wymbs et al., 2013), and limited mechanistic understanding of stuttering and fluency in PWS (Etchell et al., 2018), pose significant complications and obstacles for tDCS and tACS being ubiquitous methods for treatment of stuttering.

In order to overcome the aforementioned limitations of neurostimulation work, it is possible to use neurostimulation approaches which focus on using neural activity to guide stimulation within state-dependent or closed-loop protocols (Guerra et al., 2017; Thut et al., 2017). Within such protocols, neural activation patterns inform stimulation timing and

parameters, providing a basis for individualised treatment protocols (Thut et al., 2017; Zrenner, Belardinelli, Muller-Dahlhaus, & Ziemann, 2016). As such, neural states related to anxiety and stuttering could be determined and targeted to improve therapy outcomes.

Online EEG combined with neurostimulation can be used to guide the timing of stimulation, due to the high temporal sensitivity of EEG, and allow stimulation to be aligned to specific states of dysfunctional cortical oscillations and excitability. Offline EEG studies can allow for the determination of states of interest for stimulation, namely states which reflect the preparation or production of stuttered speech. For example, Ezzyat et al (2018) used intracranial EEG to devise patient-specific models of neural activity in order to treat memory dysfunction. In order to classify memory-related brain states, recordings from intracranial EEG data were input to a logistic regression classifier trained to discriminate encoding-related activity predictive of whether a word was later remembered or forgotten. Once individual profiles of EEG activity had devised, stimulation was applied when brain states associated with poor functioning in memory-related areas was detected. A similar approach could be used with stuttering, with non-invasive EEG recordings with abnormal CNV slope activity (Vanhoutte et al., 2016) prior to stuttered words targeted to prevent the occurrence of, or to minimise stuttering. In addition, a closed-loop approach can be taken. In a study by Ketz et al. (2018), participants took part in a task which involved finding hidden targets in novel visual scenes. EEG-tACS was then used to target oscillations important for memory retention during sleep. The use of this closed loop EEG-tACS approach led to a 48% reduction of the typical overnight drop in performance on their task. Results of this study demonstrate that closed-loop EEG-tACS is a promising approach for individualised stimulation protocols.

For stuttering, an alternative (or perhaps complementary method) for targeting the abnormal CNV activity observed in PWS could be elicitation of stuttering through a block design. Such a paradigm would contain blocks of easy and difficult stimuli that are respectively less or more likely to elicit stuttering e.g. high phonological complexity are more likely to elicit stuttering (Howell, 2011). Once such oscillatory patterns have been identified

reliably in these easy/difficult blocks, neurostimulation could be applied within the difficult blocks (where higher stuttering is expected) to entrain oscillatory activity towards patterns those observed in the easy blocks, where lower stuttering is expected.

Whilst such state-dependent and closed-loop methods of neurostimulation are in their infancy, individualised treatment protocols are likely to lead to an optimal approach for stuttering treatment in future work. In Chapter 6 we suggested future tDCS work would probably require homogenous samples, consisting of moderate to severe PWS, for tDCS to elicit stuttering reduction. Such an approach is not ecologically valid nor representative as research demonstrates more PWS present with mild stuttering rather than moderate or severe (Wingate, 2002). State-dependent and/or closed-loop approaches would therefore allow for the development of protocols which do not exclude any PWS from treatment.

Future research with online and offline EEG is needed to examine the specific states of dysfunctional cortical oscillations and excitability associated with stuttering. Literature provides some promising oscillatory targets such as CNV slope (Vanhoutte et al., 2016) which are linked to stuttering but such findings have yet to be replicated. It is further important to conduct such research across contexts and situations, to understand the role of the LIFG in PWS when speaking across different styles e.g. face to face or alone with themselves, and which may involve varying levels of anxiety. Such research would also allow us to build reliable individual profiles of a PWS' stuttering related, and situation related, neural activity. These profiles could further be refined based on levels of high and low anxiety a person experiences, which are states which can present with differential functional neural activity (Martin, Ressler, Binder & Nemeroff, 2010), and consequently may result in differential effects of NIBS. Once defined, these individual profiles of stuttering would be targeted to reduce stuttering. An individualised approach to stuttering treatment could therefore allow the development of stimulation protocols which, when combined with an appropriate fluency enhancing intervention, result in significant and lasting stuttering reduction which transfers to real-world settings.

7.4.5 Clinically relevant therapeutic outcomes. Due to the limited, and inconsistent effects, of treatment options currently available to PWS, development of interventions of high clinical relevance are of the utmost importance. Whilst results in this thesis demonstrate tDCS is a promising method to reduce stuttering in PWS, an outstanding question is whether such reductions (i.e. around 3-4% reduction in stuttered syllables) would be clinically relevant.

Onslow (2000) described mild stuttering to be speech containing less than 5% of syllables stuttered, mild-to-moderate being 5-10% syllables stuttered, moderate being 10-15% syllables stuttered, moderate to severe being 15-20% syllables stuttered and severe stuttering to be more than 20% syllables stuttered. A reduction of 3-4% stuttered syllables therefore falls just short of the reduction necessary to move a PWS from one end of a severity classification to a less severe classification i.e. severe to moderate, which could be achieved with a 5% reduced in stuttered syllables.

However, Constantino et al. (2016) demonstrated that stuttering variation in PWS can be as large as 23% across different speaking tasks (conversation, monologue, picture naming, repeated passage reading and novel passage reading) on different days (measured on 5 days over a 14-day period) in the same person. Therefore, it is possible for a PWS to present with mild stuttering on one day and moderate or severe stuttering on another day through natural variation of stuttering severity. For example, participant 5 in Constantino et al. (2016) presented with 10.20% syllables stuttered (moderate) on day one, which reduced to 3.80% syllables stuttered (mild) on day 2 and increased to 12.93% (moderate) on day three. Participant 5 therefore presented with a 6.4% reduction in syllables stuttered between day one and day two, and a 9.13% increase in syllables stuttered between day two and three. The daily variation of stuttering in PWS can therefore vastly exceed the percentage syllables stuttered reduction achieved by tDCS-based intervention, seen both in our study and in Chesters et al. (2018). The level of daily variation of stuttering also seems to exceed the percentage improvement (around 5%) reported in reviews of stuttering treatment outcome studies (Bothe, Davidow, Bramlett, & Ingham, 2006). In Chapter 5, the highest

percentage of syllables stuttered prior to intervention was 19.4% %SS in the speaking assessment and 35.60% in the reading assessment. Would a reduction of 3-4% stuttered syllables be clinically relevant for such individuals? It would be of benefit to mild PWS (<5% stuttered syllables) but perhaps less so to those who experience severe stuttering. In addition, if natural daily variation of stuttering exceeds intervention effects, can the intervention itself be considered clinically relevant? Individual differences in stuttering severity and natural daily stuttering variation is therefore problematic for determining the percentage stuttered syllables reduction which would be clinically relevant.

Across participants in Constantino et al. (2016), the average of overall percentage of syllables stuttered, across all measurement times, was 10.79%. A reduction of around 10% would enable PWS to move from the extreme of one stuttering severity classification to the lower end of a less severe classification, according to the criteria by Onslow (2000). For example, a reduction from 20% to 10% syllables stuttered would represent a change from severe to moderate stuttering. The stuttering variability observed by Constantino et al. (2016) was also correlated to life impact, indicating increased variability of stuttering was linked to reduced quality of life. Therefore, it could be argued that a reduction of around 10-11% of syllables stuttered is what is required to produce clinically relevant stuttering reduction. This is because such a reduction in stuttering severity would mitigate the average daily variation of stuttering and would consequently negate the impact of stuttering variability on life impact. A 10-11% reduction in stuttered syllables is therefore likely to reduce stuttering as well as improve quality of life. To ensure clinical relevance, a measure of daily variability could be calculated for each individual prior to intervention, using the methods of Constantino et al. (2016). This percentage daily variability of stuttering could then be used as the threshold at which stuttering reduction is considered clinically relevant for that particular PWS.

7.5 Summary

This thesis demonstrated tDCS is a promising adjunct, alongside challenging tasks and current interventions, for improving speech production processes in TS and PWS. Whilst results are promising, they require extension, validation and further exploration through further research, particularly using neuroimaging. With PWS in particular, the study in Chapter 5 is only the second study to date which has used tDCS to enhance intervention outcomes and reduce stuttering in PWS. Furthermore, the study presented in Chapter 6 is the first study to examine neural activity in PWS within ecologically valid environments. Significant future work is therefore required to understand the mechanisms of stuttering, particularly within ecologically valid settings. Such research would lead to increased understanding of mechanisms of stuttering and its reduction, and subsequent optimisation of tDCS protocols and effects. With future work and refinement, neurostimulation methods such as tDCS provide promise for enhancing the positive effects of challenging stuttering interventions. As such, augmenting stuttering interventions with neurostimulation may lead to greater, longer-lasting, and generalisable reductions in stuttering.

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