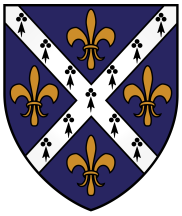
Enhancing Speech Fluency using Transcranial Direct Current Stimulation



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“My stuttering feels like an acknowledgment, in conversation, of the framework of unacknowledged complexity that surrounds the simplest exchange of words.”

From “Self-Consciousness”, the memoirs of John Updike,
Pulitzer prize-winning author, and literary critic

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Abstract

Producing speech is a highly complex task, involving the integration of sensory and linguistic information, with the precise, high-speed, co-ordination of muscles controlling breathing and the movement of the vocal folds and articulators. In spite of this complexity, producing fluent speech – moving smoothly from one speech sound to the next – can appear effortless. Speech fluency is highly socially valued, and the personal and societal costs of living with a disorder of fluency, such as developmental stuttering, are considerable. The outcomes of behavioural therapies to increase fluency are limited, however, especially for those seeking treatment in adulthood.

The overarching aim of this thesis was to investigate how anodal transcranial direct current stimulation (A-TDCS) can be used to increase speech fluency, with a particular focus on the potential application to developmental stuttering. A-TDCS is a noninvasive brain stimulation technique that can enhance the effects of motor, speech, and language training.

First, in a series of single-session experiments in typically fluent speakers, I demonstrated that applying A-TDCS over the left inferior frontal cortex Cortical oscillations are likely candidates for segmentation and coding of continuous speech. Here, we monitored continuous speech processing with magnetoencephalography (MEG) to unravel the principles of speech segmentation and coding. We demonstrate that speech entrains the phase of low-frequency (delta, theta) and the amplitude of high-frequency (gamma) oscillations in the auditory cortex. Phase entrainment is stronger in the right and amplitude entrainment is stronger in the left auditory cortex. Furthermore, edges in the speech envelope phase reset auditory cortex

oscillations thereby enhancing their entrainment to speech. This mechanism adapts to the changing physical features of the speech envelope and enables efficient, stimulus-specific speech sampling. Finally, we show that within the auditory cortex, coupling between delta, theta, and gamma oscillations increases following speech edges. Importantly, all couplings (i.e., brain-speech and also within the cortex) attenuate for backward-presented speech, suggesting top-down control. We conclude that segmentation and coding of speech relies on a nested hierarchy of entrained cortical oscillations. increased speech motor learning relative to a sham control, but did not improve consolidation of this learning (chapter 2). Furthermore, I found that neither increasing stimulation intensity from 1 mA to 2 mA, nor changing from a uni-hemispheric to a bi-hemispheric configuration, had an additional effect on learning.

Next, in single-session study with adults who stutter, I assessed the feasibility of using A-TDCS to improve fluency (chapter 3). Fluency was temporarily induced, by speaking in unison with another person, but the concurrent application of 1 mA uni-hemispheric A-TDCS over left inferior frontal cortex did not significantly prolong this fluency. Nevertheless, a trend towards stuttering reduction gave some indication that fluency might be increased using a multiple-session approach. Furthermore, I gained a number of important insights from these single-session studies, which I used to inform the design of the final multiple-session trial.

In this final study, I completed a randomised controlled trial in 30 adult males with moderate to severe stuttering. Participants were randomized to receive either 1 mA A-TDCS or sham stimulation over left inferior frontal cortex combined with temporary fluency inducing behavioural techniques, for 20 minutes a day over 5 days

(chapter 4). A-TDCS significantly reduced disfluency for at least 5 weeks following this intervention. The effect was specific to the speech impairment of development stuttering, as measures of the psycho-social consequences of stuttering were not modulated by A-TDCS.

The findings of these studies offer significant promise for the future application of noninvasive stimulation as an adjunctive therapy for adults who stutter. In the concluding chapter, I discuss the important implications of my findings for the future use of this technique.

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List of abbreviations

% ds: percentage of disfluent syllables

% ss: percentage of stuttered syllables

A-TDCS: anodal transcranial direct current stimulation

BA44: Brodmann area 44

C-TDCS: cathodal transcranial direct current stimulation

DTI: diffusion tensor imaging

fMRI: functional magnetic resonance imaging

IFC: inferior frontal cortex

M1: primary motor cortex

MEG: magnetoencephalography

OASES: overall assessment of the speakers experience of stuttering

RCT: randomised controlled trial

SOR: supra-orbital ridge

SSI-3: stuttering severity instrument, version 3

SSI-4: stuttering severity instrument, version 4

TDCS: transcranial direct current stimulation

TFI: temporary fluency inducing

TMS: transcranial magnetic stimulation

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Chapter 1

General Introduction

1.1 Speech fluency

Speech is considered fluent when there is a perception of 'smoothness', or an effortless flow in the transitions between speech sounds. The pattern of typical conversational speech, however, is regularly punctuated by moments of disrupted fluency (or disfluency). Disfluencies may mark pauses for thought, the search for a correct word to express the speaker's exact meaning, or disrupted linguistic or speech motor planning in response to external stressors (such as presence of an audience, or interruptions from a conversational partner).

Developmentally, periods of increased speech disfluency may occur between the ages of two and a half to four years (Guitar, 2014). During this time speech motor skills are developed and refined (Williams & Stackhouse, 1998), language skills rapidly expand (Kuhl, 2004) and vocal tract morphology undergoes significant change (Vorperian et al., 2005); any or all of which may influence fluency. In adults, hesitations are more likely prior to less predictable words (Beattie & Butterworth, 1979), and have been associated with repair of speech planning prior to articulation (Postma & Kolk, 1993). In addition, disfluencies increase during the normal aging process (Searl, Gabel & Fulks, 2002).

The ability to maintain fluency implicates efficient co-ordination of cognitive and linguistic processes, but is critically dependent on the sensorimotor components of speech production. Unusual patterns of disfluency, either in frequency or type, are associated with various speech and language disorders. Fluency disturbances may occur as one symptom of a more general disorder, for example in nonfluent aphasia, or dystonia. However, there is also a family of disorders in which disfluency is the

defining characteristic, which includes developmental stuttering (also known as stammering), acquired stuttering and cluttering.

1.2 Developmental Stuttering

1.2.1 Presentation and prevalence

Developmental stuttering typically emerges around three years of age and affects one in 20 children, with a male to female ratio of 2:1 (Yairi & Ambrose, 1999). There are high levels of recovery during childhood, particularly in girls, which may occur spontaneously or supported by clinical intervention. However, one percent of the adult population has a persistent developmental stutter, with the gender bias in both emergence and recovery from stuttering meaning four times as many men than women are affected (Yaruss & Quesal, 2004).

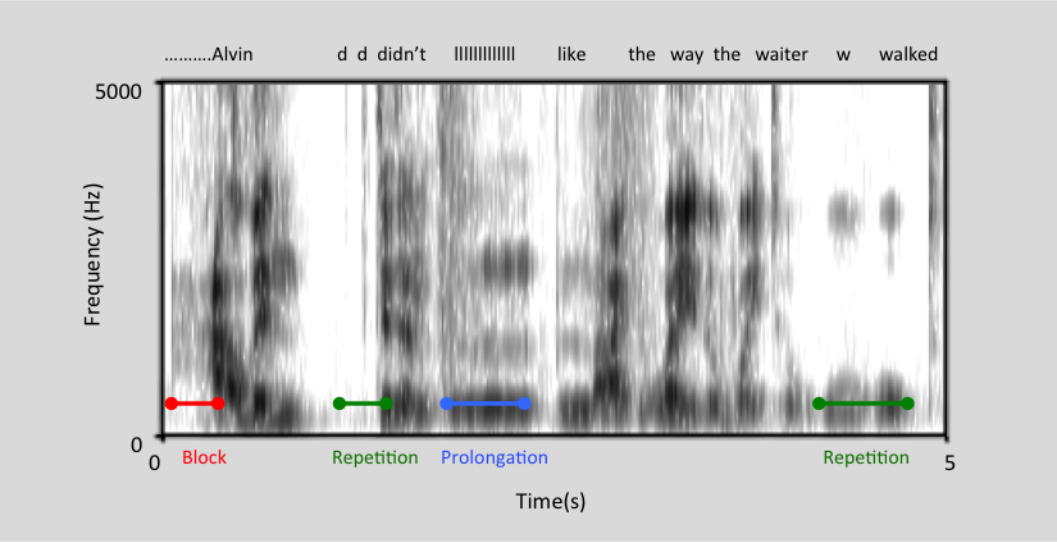
The clinical description of developmental stuttering used by Speech and Language Therapy professional bodies (e.g. Royal College of Speech and Language Therapists, American Speech-Language-Hearing Association) encompasses the primary characteristics of overt speech disruptions, secondary characteristics that may emerge in response to stuttering, and the psycho-social consequences of living with the condition.

Primary characteristics

Developmental stuttering is primarily characterised by intermittent disruptions to the flow of speech that are distinct from the typical disfluencies experienced by all speakers. A triad of particular disfluencies occur in stuttered speech: 'blocks' in which no sound is produced, the repetition of phonemes or syllables, and abnormally prolonged phonemes or syllables. Figure 1 visualises these primary characteristics in a spectrogram, showing the distribution of acoustic energy as a person who stutters produces a sentence "Alvin didn't like the way the waiter walked". There is a delay

before the first word in the sentence is produced, marked by a low-amplitude band of acoustic energy that would be heard as a “creaking” voice. This is a block in the flow speech, i.e. a tense pause, and although some voicing is produced in this case, often these blocks are inaudible. A prolongation can be seen as a long band of higher-amplitude energy on the “l” sound of the word “like”. Repetitions of the first sounds of the words “didn’t” and “walk” appear as brief bursts of energy.

These moments make up a minority of all speech sounds (e.g. a person with a moderate stutter will produce approximately 85 to 90 % of their speech fluently), however, they are perceived as significant disruptions to the flow of speech. Stuttered moments are not randomly distributed in the speech stream: it is far more common to stutter at the beginning of words or sentences (Wingate, 2002), suggesting the initiation of, and transitions between, speech movements may be problematic in developmental stuttering.



The sentence is transcribed above the spectrogram. Disfluencies are indicated by coloured bars, and labelled below the spectrogram. Red = block. Green= repetition. Blue = prolongation. This visual representation of the sentence shows the variation in frequencies (y-axis) in the acoustic signal across time (x-axis), with the amplitude (loudness) of the signal indicated by the intensity of the greyscale.

Figure 1: Sound spectrogram of a sentence spoken by an adult male who stutters

Secondary characteristics

The core speech disruptions are often accompanied by additional or secondary behaviours, which may be voluntary or involuntary. For example, abnormal muscular tension in the face or extraneous movements of the head or body may accompany stuttered moments, and present similarly to tics. Sometimes voluntary body movements develop as a conscious strategy to progress through a stuttered moment (particularly if these movements are rhythmic). Over time, people who stutter often recognise patterns in the occurrence of stutters, and may develop strategies to avoid problematic speech sounds. This can increase the number of other disfluencies in a person's speech (e.g. the use of fillers such as "um", or phrase revisions) but often there is no overt sign of avoidance (Bloodstein, 2008). Secondary characteristics may

significantly contribute to the maintenance of stuttering, and to the fear of stuttering, and so are important to understand and tackle in therapy.

Psycho-social consequences

The negative consequences of living with a stutter can be far-reaching. Social anxiety or shyness were long posited as a factor in the aetiology of stuttering. Following prospective studies (Yairi & Ambrose, 2013; Reilly et al., 2009), we now understand that this is not the case. However, social anxiety has been associated with living with a stutter, and it is likely that this symptom emerges in response to continued negative associations with speaking situations (Iverach et al., 2009; Iverach et al., 2011; de Carle & Pato, 1996; Blumgart, Tran & Craig, 2010). Developmental stuttering has also been associated with reduced educational (O'Brian et al., 2011) and occupational outcomes (Klein & Hood, 2004) and quality of life (Craig, Blumgart & Tran, 2009), and increased experience of social stigma (Logan & O'Connor, 2012; Bricker-Katz, Lincoln & McCabe, 2009; Bricker-Katz, Lincoln & Cumming, 2013).

1.2.2 Increasing fluency in developmental stuttering

Speech and language therapy for developmental stuttering

Therapeutic techniques for reducing overt moments of stuttering emerged from two distinct schools: fluency shaping (Webster, 1982) and stutter modification (Van Riper, 1973). Current clinical practice often combines techniques from both schools. Fluency shaping aims to train an alternative speech pattern which should be used at all times, to decrease the occurrence of stuttered moments. This pattern typically includes prolonging all phonemes, using gentle onsets to phonemes (for example, reducing the build-up of pressure preceding plosives sounds such a ‘p’) and

increasing the use of voicing, or phonation (such that a word with typically unvoiced consonants, like “pat”, sounds more like “bad”) (O'Brian et al., 2003; Webster, 1982; Boberg & Kully, 1994). Stuttering modification is motivated by a psychological model aimed at reducing fear of stuttering, and so producing ‘easy’ tension free stuttering (Van Riper, 1973). It includes techniques that should be used only preceding or during stuttered moments, such as pausing, reducing orofacial tension and continuing at a slowed rate.

Although motivated by different theoretical backgrounds, both approaches involve modification of speech motor behaviour. Novel speech patterns are used, which may lessen the burden on the speech motor system by reducing the complexity of transitions between phonemes, slowing speech rate and reducing physical tension. However, these patterns often compromise speech naturalness, which can result in a more negative listener response than to stuttering itself (Stuart & Kalinowski, 2004). In addition, the effort involved in maintaining fluency techniques is associated with a high level of relapse following treatment (Craig & Hancock, 1995). Benefits do not persist without continued training and practice (Kell et al., 2009; Ward, 2006) making long-term fluency increases difficult to achieve. Even when techniques are regulary practised, they may simply become less effective over time (Ward, 2006). A recent systematic review of stuttering interventions showed considerable individual variability in response to therapeutic approaches to stuttering, with no clear dose-response relationship (Baxter et al., 2016). The authors highlighted the need for a better understanding of the mechanisms of action involved in these interventions, in order to increase therapy outcomes.

In current speech and language therapy practice, the focus of intervention typically shifts in late childhood, when the likelihood of recovery lessens, toward managing the consequences of living with a stutter. The need for interventions addressing the psycho-social outcomes of young people and adults who stutter is clear (Boyle, 2013; Helgadottir et al., 2014; Beilby, Byrnes & Yaruss, 2012). However, the lack of long-term effectiveness of therapy directly targeting overt stuttering in adults has also motivated this shift of focus. Therefore, research into improving outcomes of fluency therapy, which could be offered alongside psycho-social interventions, is important.

Temporary fluency induction in developmental stuttering

In addition to the techniques used in speech and language therapy to enhance fluency in developmental stuttering, there are numerous methods for the temporary induction of fluency, which have been investigated since the 1950s (e.g. Cherry & Sayers, 1956). These techniques have the benefit that they result in a striking and immediate increase in fluency, however, this effect is reversed when the person who stutters returns to a habitual speaking pattern.

Temporary Fluency Induction (TFI) methods include changing sensory feedback regarding speech, for example delayed auditory feedback, frequency altered feedback, immediate or delayed visual feedback, vibrotactile feedback, or auditory masking (See Lincoln, Packman & Onslow, 2006 for a review of auditory feedback effects; visual feedback: Kalinowski et al., 2000; Snyder et al., 2009b; vibrotactile feedback: Snyder et al., 2009a). In contrast, in people who do not stutter, delaying sensory feedback disrupts speech accuracy and rate (e.g. Chesters, Baghai-Ravary & Möttönen , 2015). TFI techniques also include altering habitual speaking patterns,

either spontaneously or by matching to an external signal, e.g. using an accent, speaking in time with a metronome (Davidow, 2014), choral or unison speech (Kalinowski & Saltuklaroglu, 2003a) and singing (Healey, Mallard & Adams, 1976). In addition, fluency can increase when speaking to infants or animals. These effects are likely mediated by reduced pragmatic communicative demands, however child- and pet-directed speech also have altered rate, rhythm and prosody (Fernald & Kuhl, 1987; Burnham, Kitamura & Vollmer-Conna, 2002).

There has been limited translation of effects into clinical settings, as the temporary nature of these effects reduces their clinical utility. Delayed auditory feedback devices are available commercially as speech prostheses, although, like fluency therapy, there is evidence that the effects "wear off" over time. For example, a phase I clinical trial of an altered auditory feedback prosthesis showed that, although fluency improved immediately after fitting, there was no significant benefit measured across a 4-month period of use (Pollard et al., 2009). Metronome-timed speech has also been used clinically, by modeling a change in speech rhythm, which is then used in the absence of the external stimulus (Andrews, 1965; Coppola & Yairi, 1982; Trajkovski et al., 2009; Trajkovski et al., 2011). Used in this way, it is similar to the fluency-shaping, prolonged speech method, and has similar cost to naturalness.

TFI and theories of developmental stuttering

The mechanisms underlying TFI effects are not well understood. However, there are common characteristics, some of which overlap with techniques used in fluency-shaping therapy, which offer insight into the abnormal processes involved in developmental stuttering. The benefits of changing sensory information about speech

have informed theories regarding abnormal sensorimotor integration for speech in developmental stuttering. For example, an early computational model posited abnormal 'internal modelling' of the desired sensory consequences of speech movements during speaking, a process which is developed and maintained by using sensory feedback (Neilson & Neilson, 1987) (a more recent neurocomputational model, developing this idea, is discussed in section 1.3.5.). Introducing an external delay to incoming sensory information may realign the internal model to some salient factor (e.g. the syllable). However, it is also possible that disturbing sensory feedback results in that source of information being disregarded. If integration of sensory feedback is impaired, ignoring the feedback signal could lead to improved speech fluency. Enhancing sensory feedback in other modalities (e.g. visual or somatosensory), may serve to override erroneous auditory feedback. It has also been suggested that choral speech, and altered auditory feedback, recruit a 'mirror neuron' system for imitating speech, which bypasses the pathological speech process in developmental stuttering (Kalinowski & Saltuklaroglu, 2003c).

The changes to habitual speaking pattern that increase fluency in people who stutter include modifying articulation, voicing, speech rhythm and rate. Several theories implicate difficulty with the temporal aspects of speech control in developmental stuttering (e.g. Ludlow & Loucks, 2003; Karniol, 1995.) There has been considerable focus on the importance of reducing speaking rate, and it is intuitive that such a reduction would support temporal co-ordination of the various processes involved in fluent speech. However, slowed rate is not critical to fluency induction, as TFI is also effective at fast speaking rates (e.g. Hudock et al., 2010; Kalinowski & Stuart, 1996; Glover et al., 1996). Increasing the duration of voiced sounds (during which the vocal

folds vibrate), or substituting unvoiced for voiced sounds (e.g. producing a word like "tickle" to sound more like "diggle") may decrease the load on co-ordinating speech movements by reducing the frequency of voicing transitions. Using longer voiced intervals also increases auditory (and vibrotactile) speech feedback, which could support sensorimotor integration. Finally, it is a possibility that any change from a habitual speaking pattern is sufficient to increase fluency.

In summary, there is consistent behavioural evidence from techniques to increase fluency, that developmental stuttering involves disruptions in the timing of speech movements, and in sensorimotor integration for speech.

1.3 Brain differences associated with developmental stuttering

There is a growing body of research studies investigating the neurobiological and neurophysiological correlates of developmental stuttering. Much of the data are consistent with the views that a dysfunction in timing of speech movements, or in integrating sensory information regarding speech, are implicated in the condition. Numerous regions within the motor speech network are affected in developmental stuttering, and the left IFC plays an important role within this network.

1.3.1 Abnormal structure and function of inferior frontal cortex

Over-activation of the right frontal operculum, the anterior insula or both, was noted as one of three neural signatures of developmental stuttering in the earliest meta-analysis of functional imaging (positron emission tomography: PET, and functional magnetic resonance imaging: fMRI) studies (Brown et al., 2005). Two more recent meta-analyses replicated the finding that an over-active right IFC is one marker of the trait of stuttering (Budde, Barron & Fox, 2014; Belyk, Kraft & Brown, 2015).

Under-activity in the left IFC regions during speaking has also been shown in several functional imaging studies in developmental stuttering, with some variation of the exact location affected (Wu et al., 1995; French et al., 2011; Fox et al., 1996; Neumann et al., 2005; Watkins et al., 2008; Toyomura, Fujii & Kuriki, 2011). In addition, resting-state functional connectivity is also reduced in this region, in adults who stutter, and a short-term intervention did not "normalise" this connectivity (Lu et al., 2012). It has been suggested that right-hemisphere over-activation may reflect compensation for a primary deficit in left IFC (Kell et al., 2009; Braun et al., 1997; Neef et al., 2011a). A recent study investigating the activation and connectivity of the

posterior sections of left BA44, showed under-activity within left dorsal posterior BA44 during imagined speech (and humming) in adults who stutter (Neef et al., 2016). Posterior IFC regions have been associated with highly automated language production tasks, in contrast to anterior regions, which take a role in more controlled processes (Jeon & Friederici, 2013). Impairment in the ability to produce the highly automated motor plans for speech has been suggested in DS (e.g. Alm, 2004), which would specifically implicate posterior left IFC (i.e. BA44, Neef et al., 2016). Neef and colleagues (2016) also found that the increased right homologous BA44 activation had a slightly delayed time course relative to left hemisphere activity. As right IFC activation is associated with motor inhibition (Aron, Robbins & Poldrack, 2014), this was hypothesised to reflect an excessive motor stopping response in developmental stuttering, i.e. a potential causal, rather than compensatory, process in the condition.

Diffusion tensor imaging (DTI) studies have identified disruption in white matter integrity within the left IFC. Sommer and colleagues (Sommer et al., 2002), in the first DTI study in adults who stutter, found reduced fractional anisotropy in the white matter underlying sensorimotor representation of the tongue and larynx, and argued that the resulting disconnection to left inferior frontal and ventral premotor cortex (i.e. disruption to the arcuate fasciculus) was critical to the speech production difficulties in developmental stuttering. White matter disruption in the left arcuate fasciculus close to the Rolandic operculum has been replicated in children (Chang et al., 2008), and in a slightly anterior location (underlying ventral premotor cortex) in young adults with developmental stuttering (Watkins et al., 2008). The study by Watkins and colleagues (2008) identified under-activity during speaking in the left ventral premotor cortex directly overlying the white matter disruption. They

suggested that this structural deficit may affect both the integration of sensory and motor information for speech, and the translation of speech plans into executed movements.

1.3.2 Underactive auditory cortex activation

Reduced auditory cortical activation during speech has also been described as a 'neural signature' of developmental stuttering (Brown et al., 2005; Belyk et al., 2015; Budde et al., 2014). In models of motor control, a copy of the motor command (an efference copy) is sent to the sensory systems during movement. Brown et al (2005) argued that the speech disruptions in stuttering could increase efference copy, leading to excessive 'driving down' of auditory activation. Direct measurement of the speech-induced suppression response in auditory cortex during speech (using magnetoencephalography: MEG) has not shown greater suppression in adults and children who stutter, than in those who do not (Beal et al., 2010; Beal et al., 2011). However, there is a delay in this suppressive auditory response in developmental stuttering (Beal et al., 2010; Beal et al., 2011), and also a lack of attentuation of auditory responses prior to speaking, i.e. during planning of speech movements (Daliri & Max, 2015). This electrophysiological evidence, then, is consistent with a deficit in sensorimotor integration in developmental stuttering, potentially affecting the timing of this integration.

In addition, impairments are seen in developmental stuttering in the ability to process auditory information, specifically rhythmic information, independently of a speech production task. For example, discrimination of auditory rhythms is impaired in children who stutter (Wieland et al., 2015), and entrainment of beta-band

oscillatory activity to such rhythmic stimuli is disrupted (Etchell et al., 2016). Neural activity with the beta frequency range has been linked to motor processing and formulation of internal models of movement goals (Cheyne, 2013). This suggests abnormal auditory cortex involvement during speech in developmental stuttering, which may reflect sensor-motor integration deficits, temporal processing difficulties, or both.

1.3.3 Cerebellar abnormalities

The cerebellum receives input from the motor cortex and the periphery, and integrates this sensory and motor information to predict the consequences of motor acts (Wolpert, Miall & Kawato, 1998). These predictions can be compared to feedback regarding ongoing movement and the difference (the error signal) used to refine motor plans. Adults who stutter have disrupted white matter integrity within the cerebellum: reduced fractional anisotropy is evident in all three sets of cerebellar peduncles, i.e. those that receive sensory and motor inputs, and also those that output to the cortex (Connally et al., 2013).

Over-activation of the cerebellar vermis was the third neural signature identified in the original meta-analysis of functional imaging studies (Brown et al., 2005). Over-activation of the cerebellum when adults who stutter speak may reflect increased error detection, due to mismatched predictions and feedback signals. The recent meta-analyses (Belyk et al., 2015; Budde et al., 2014) made a distinction between the state (overt moments of stuttering) and the trait of stuttering (comparing people who stutter with people do not stutter, during fluent speech). Using this division, over-activation of the cerebellar vermis was specifically related to moments of disfluency,

i.e. the stuttering state (Belyk et al., 2015; Budde et al., 2014). In addition, one of the meta-analyses associated the stuttering trait with under-activity in the cerebellar vermis (Belyk et al., 2015). Consistent with cerebellar overactivity being associated with moments of stuttering, following successful fluency-shaping intervention (De Nil et al., 2003b), and during TFI (Fox et al., 1996), cerebellar activity reduces during speaking.

1.3.4 Basal ganglia function

Abnormal basal ganglia activation was only reported in one of the three meta-analyses of developmental stuttering (over-activation of left globus pallidus during stuttered speech: Belyk et al., 2015). However, basal ganglia dysfunction is shown in many neuro-imaging studies of developmental stuttering, implicating several nuclei (Fox et al., 1996; Giraud et al., 2008; Watkins et al., 2008). In addition, severity of stuttering symptoms correlates with basal ganglia activity (specifically in the caudate nuclei bilaterally: Giraud et al., 2008), and basal ganglia activation decreases following intervention (Giraud et al., 2008; Ingham et al., 2013), and during TFI (e.g. choral speech: Fox et al., 1996).

The alleviation of stuttering symptoms by provision of an external rhythm is similar to the improvement in initiation of movements and "gait fluency" seen for movement disorder in Parkinson's disease (Glickstein & Stein, 1991), further strengthening the evidence for basal ganglia dysfunction in developmental stuttering. However, investigations of the role of dopamine in disfluency in developmental stuttering reveal that this relationship is complex (Wu et al., 1997; Alm, 2004). Disfluency has been related both to increases and decreases of dopamine metabolism, which may

reflect that dopamine availability should have a certain balance to support fluency, and that developmental stuttering could equally result from excessively high or low levels.

1.3.5 Disrupted connectivity in the speech system in developmental stuttering

It is clear from the studies described in the preceding sections, that the speech fluency disruptions seen in developmental stuttering are associated with abnormalities across the speech motor network. Studies of structural and functional connectivity, and neuro-computational accounts, have proposed network-level theories concerning the aetiology of developmental stuttering, which support the evidence reviewed above.

Abnormal structural connectivity across a fronto-parieto-temporal cortical network has been identified. A study combining DTI meta-analysis, and tractography through the identified clusters, revealed consistent reductions of white matter integrity in developmental stuttering within the left superior longitudinal fasciculus, including part of the arcuate fasciculus (Neef, Anwander & Friederici, 2015a). The affected tracts connect inferior frontal regions with parietal, and temporal cortex. Fibres running through the posterior midbody of the corpus callosum, to connect sensorimotor cortices in the two hemispheres were also consistently disrupted (Neef et al., 2015a).

An obvious consequence of this disrupted structural connectivity is the impaired ability to co-ordinate the function of regions connected by these tracts. Impaired functional connectivity between sensory and motor output regions during speech has

been demonstrated. For example, people who stutter showed negative correlation of auditory and motor activation during speech (Watkins, 2011), and reduced coupling of left dorsal posterior BA44 with parietal cortex (Neef et al., 2016). Functional connectivity between left BA44 and ventral pre-motor cortex is also reduced (Chang et al., 2011), again implicating progression from planning to executing speech movements. The left-lateralised excitability of oro-facial motor cortex is reduced in adults who stutter relative to typically fluent speakers (Neef et al., 2011b; Neef et al., 2015b). This lack of left-lateralisation of motor activation is consistent with less efficient communication between the left IFC and motor cortex, which affects the timely planning of motor sequences. This is further supported by a study using MEG to measure the timing of brain activity during single word reading, which showed that adults who stutter activate left motor cortex prior to left IFC, a reversal of the timing seen in fluent speakers (Salmelin et al., 2000).

Disrupted connectivity between cortical and subcortical structures is also implicated in developmental stuttering, with regions in the left IFC playing an important role. Basal ganglia connectivity has been suggested as a core deficit (Alm, 2004; Smits-Bandstra & De Nil, 2007). The cortico-striato-thalamo-cortical network is important for the automatisation of complex motor sequences. Difficulty automatising skills during learning has been shown in developmental stuttering (Smits-Bandstra et al., 2007), and the idea that the neural substrate for highly automated speech sequences is affected was also revisited in a recent study of posterior BA44 connectivity, as mentioned in section 1.3.1. (Neef et al., 2016).

Alm (2004) hypothesized that the output from the putamen to the supplementary motor area is critically impaired in developmental stuttering, leading to a compromised ability to generate internal timing cues for speech. Both the basal ganglia (as described in section 1.3.4.) and supplementary motor area show abnormal activity patterns in the condition (Fox et al., 1996; Giraud et al., 2008; Watkins et al., 2008). Using evidence from studies in Parkinson's disease (e.g. Cunnington, Bradshaw & Iansek, 1996), it was suggested that a compensatory route to speech fluency can be recruited when an external timing cue is used (e.g. in metronome-timed speech), or when an internal cue is generated for movement that is not highly automated (e.g. in fluency-shaping therapy: Alm, 2004). This compensatory route involves the lateral premotor cortex, which receives input from the cerebellum (Alm, 2004). This theory fits with much of the behavioural evidence. However, one difficulty with describing premotor cortex as having a compensatory role in developmental stuttering, is the disrupted function of ventral premotor cortex, and of the white matter integrity underlying it, which seems likely part of the primary pathology in the condition (Watkins et al., 2008). Structural equation modeling of fMRI data has shown abnormalities both in connectivity between bilateral inferior frontal gyrus and right putamen, and between right cerebellum and left premotor cortex, associated with the planning and execution of speech, respectively (Lu et al., 2010).

Two related neuro-computational models that specify the processes and neural substrates responsible for speech production (DIVA: Guenther, Ghosh & Tourville, 2006; GODIVA: Bohland, Bullock & Guenther, 2010), also suggest that impaired cortico-striato-thalamo-cortical connectivity has a causal role in developmental

stuttering. The model has been used to generate predictions and compare these with neuro-imaging evidence (Civier, Tasko & Guenther, 2010; Civier et al., 2013). Similarly to earlier computational models (Neilson et al., 1987), impairments affecting the internal models guiding speech are suggested. However the various subcomponents forming these internal representations, and the translations between them, are specified in greater detail. The GODIVA model includes a cortico-striato-thalamo-cortical loop connecting the ventral premotor cortex with the basal ganglia and thalamus, involved in selecting speech sounds. Simulations affecting this circuit have resulted in speech disruptions consistent with those seen in developmental stuttering (Civier et al., 2010; Civier et al., 2013). For example, when translation of feedforward commands in motor cortex is interrupted in the model (which is a plausible consequence of the structural and functional impairment of left ventral premotor cortex), the result is syllable repetitions (Civier et al., 2010). Simulations of disrupted white matter in this pathway, and of a dopaminergic imbalance, affected the model's ability to transition between syllabic speech motor programs (Civier et al., 2013), also leading to stuttering-like disruptions.

In summary, the exact neurobiological causal mechanism underlying developmental stuttering is yet to be determined. However, there is strong evidence implicating the neural substrates involved in transition from speech planning to execution, and in sensorimotor integration. Left IFC plays a key role in these processes (Hickok & Poeppel, 2007; Guenther, 2006; Bohland et al., 2010). Supporting efficient IFC function during speech could result in the alleviation of one or more of the dysfunctional processes involved in stuttering. There are several theoretical arguments identifying left IFC pathology as causative in developmental stuttering.

However, even if such theories prove incorrect, IFC may be an accessible ‘gateway’ to improving function of connected brain regions.

1.4 Transcranial direct current stimulation

A possible method for altering activation within left IFC, to increase speech fluency, is to use noninvasive brain stimulation. Transcranial direct current stimulation (TDCS) is a method for modulating cortical excitability, which has been used to increase learning when combined with a task. As it is inexpensive, safe, and well tolerated, TDCS has attracted research interest as a potential tool for use in neuro-rehabilitation.

1.4.1 Physiological mechanism of TDCS

TDCS involves passing a weak electric current, of 1 or 2 mA, between two electrodes, which are placed on the scalp. A proportion (about 10 %: Miranda, Lomarev & Hallett, 2006), of the current passes through the skull and underlying cortex, and modulates neuronal excitability by shifting the resting membrane potential of stimulated neurons. The direction of excitability change depends upon current direction; the anode increases and the cathode decreases cortical excitability (Nitsche & Paulus, 2001; Nitsche et al., 2003b).

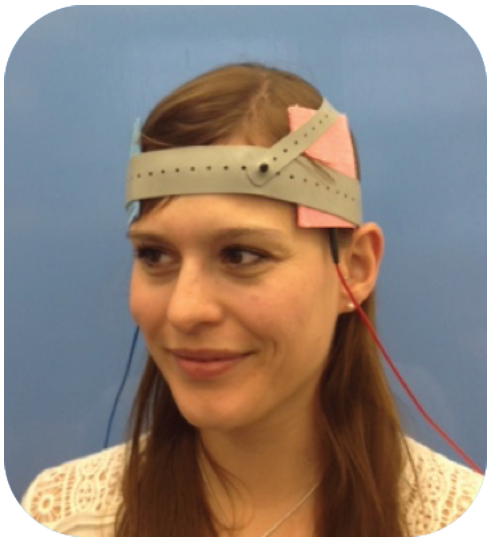
The early (and numerous subsequent) TDCS studies involved stimulation of the primary motor cortex (M1). This allowed changes in excitability to be demonstrated using transcranial magnetic stimulation over the stimulated cortex, eliciting motor-evoked potentials. During TDCS, changes in excitability do not have any significant effect on synaptic plasticity. However, the after-effects of TDCS modulate glutamatergic (anodal and cathodal) and GABAergic (anodal only) synapses (see Stagg & Nitsche, 2011b for review). The plasticity induced by TDCS is similar to the plasticity induced by motor learning, and the interaction of the two mechanisms

results in an increase in magnitude and duration of learning effects (Bikson, Name & Rahman, 2013; Stagg et al., 2011a). The interaction of TDCS with learning is limited by homeostatic mechanisms that ensure that neural plasticity remains within a stable range (Lang et al., 2004; Amadi et al., 2015). For example, the excitability induced by 13 minutes of A-TDCS is reversed if stimulation continues for 26 minutes (Monte-Silva et al., 2013). Typical TDCS protocols use stimulation durations of between 10 and 20 minutes, concurrently with a task, with electrode sizes of 25cm^2 to 35cm^2. As the current intensities used across studies vary between 1 and 2 mA, current densities applied can vary between 0.003 and 0.08 mA/ cm^2. There is an assumption in some studies (particularly those with clinical populations) that higher current densities yield greater effects. However, increased current density does not consistently increase excitability (see Nitsche et al., 2003c, and Kidgell et al., 2013).

Most TDCS studies have used a uni-hemispheric electrode configuration, where one electrode is placed over the cortical region of interest, and the second is placed over a region assumed to be functionally inert, such as the contralateral supra-orbital ridge (SOR), or on an extracephalic location (e.g. the shoulder). The aim of such configurations is to focus the effects of stimulation at one cortical location, although the flow of current to, or from (depending on polarity), the second electrode may also influence excitability in other regions. A bi-hemispheric configuration, where the second electrode is placed over the homologous region in the opposite hemisphere, is sometimes used if inter-hemispheric inhibition is hypothesized to be beneficial. TDCS has the additional benefit that studies can include a sham control condition, which is indistinguishable from real stimulation.

1.4.2 TDCS effects on motor and language skills

The physiological effects of TDCS cannot be mapped directly onto behavioural effects. Anodal stimulation (A-TDCS) generally increases some measure of behavioural performance, when applied concurrently with a task, in typical adults and in clinical populations. Uni-hemispheric cathodal stimulation (C-TDCS) has more variable effects. It can decrease behavioural performance, relative to sham, when applied over task-relevant cortex (e.g. Stagg et al., 2011a), or increase performance when applied over regions involved in maladaptive activity, e.g. following stroke (e.g. Kim et al., 2010). However, somewhat counter-intuitively, ipsilesional C-TDCS has improved function in aphasic stroke patients (Monti et al., 2008). In addition, numerous studies in typical adults have shown no behavioural effect of C-TDCS, suggesting that a healthy brain may be robust to the inhibitory effects of cathodal stimulation (Galea & Celnik, 2009; Vines, Cerruti & Schlaug, 2008). The studies described within this thesis apply A-TDCS to the left IFC, in either a uni-hemispheric configuration, with the cathode on contralateral SOR, or bi-hemispheric configuration, with the cathode over contralateral IFC (figure 2 shows the uni-hemispheric configuration used). The following sections will focus on the evidence for behavioural effects of A-TDCS. The studies cited use uni-hemispheric configurations, with the cathode on the contralateral supra-orbital ridge, unless otherwise specified.



Anode over left inferior frontal cortex (IFC) and cathode over right supra-orbital ridge (SOR).

Figure 2: Uni-hemispheric TDCS configuration

A single session of 1 mA A-TDCS applied over M1 can improve motor task performance and learning in typical adults (Nitsche et al., 2003c; Boggio et al., 2006a; Galea et al., 2009; Stagg et al., 2011a) and stroke patients (Hummel et al., 2005a; Hummel & Cohen, 2005b; Hummel & Cohen, 2006), compared to sham stimulation. A-TDCS over areas other than M1 can also increase performance on targeted behaviours. A-TDCS at 1- or 2 mA intensity over left IFC has increased performance in a range of language tasks in typical adults, for example, naming (Holland et al., 2011), artificial grammar learning (de Vries et al., 2010) and verbal fluency (Iyer et al., 2005). One study to date has focused on speech articulatory ability in typical adults. 2 mA A-TDCS over left IFC improved performance during, but not following, a "tongue-twister" repetition task (Fiori et al., 2014). The lack of improvement in performance following the task was surprising, however, as the effects of a single session of A-TDCS typically persist for tens of minutes following stimulation.

Many individual factors influence the behavioural response to stimulation (Wiethoff, Hamada & Rothwell, 2014; Krause & Cohen Kadosh, 2014) and single-session studies are particularly vulnerable to this variability obscuring any TDCS-modulated change. However, combining A-TDCS with a task over several consecutive daily sessions can increase the size, and persistence of effects (e.g. Hashemirad et al., 2016), which lends TDCS its appeal at an adjunctive method for use in neuro-rehabilitation.

1.4.3 Multiple-session TDCS studies

A meta-analysis of intervention studies using TDCS, delivered over several days, to support motor rehabilitation for stroke found an overall benefit of TDCS across various protocols and stages of recovery (Kang, Summers & Cauraugh, 2016), with

effects persisting for over a month, on average. For example, in one study A-TDCS to affected M1 was combined with physiotherapy for various motor impairments over 6 days, and lasting benefits were reported at 3-month follow-up (Khedr et al., 2013, n.b. contralesional C-TDCS was also effective in this study). In addition, a study conducted since the meta-analysis found A-TDCS applied over the ipsilesional M1 in combination with an arm motor rehabilitation programme delivered over nine sessions, resulted in lasting functional improvements for at least 3 months (Allman et al., 2016). The motor symptoms of Parkinson's disease can also be improved with TDCS (see Broeder et al., 2015, for review). For example, 5 daily sessions of A-TDCS to M1 of the leg reduced freezing of gait measured up to one month after stimulation, in Parkinson's disease patients (Valentino et al., 2014).

There are fewer multi-session TDCS studies of acquired speech and language conditions than motor conditions. A systematic review of RCTs using TDCS in aphasia, which prioritized evidence of functional communication improvements, found no evidence of effectiveness (Elsner et al., 2015). However, there are numerous studies showing benefits of TDCS with this population (see reviews by Holland & Crinion, 2012; Monti et al., 2013; Sandars, Cloutman & Woollams, 2016). This suggests that there is variability in the quality of studies, but sufficient positive indication to warrant further work with more stringent controls. Anomia (difficulty producing words, particularly nouns) has been improved using a combination of naming therapy and A-TDCS over left IFC for 5 daily sessions, with effects persisting at 1-week follow-up (Baker, Rorden & Fridriksson, 2010). Speech motor skill was improved in patients with acquired apraxia of speech following stroke, in two small studies using A-TDCS over left IFC. Although the small sample sizes preclude strong

conclusions, these studies show some potential for TDCS in speech motor rehabilitation. Uni-hemispheric stimulation of IFC at 1mA, combined with 5 sessions of articulatory therapy, improved accuracy of speech articulation in three patients, relative to sham, and this effect was maintained at two-month follow-up (Marangolo et al., 2011). Ten sessions of 2 mA bi-hemispheric stimulation over IFC with articulatory therapy, improved the speed and accuracy of speech in eight patients, tested one week later (Marangolo et al., 2013).

Positive outcomes of mutiple-session intervention studies affecting motor and speech function on people with acquired neurological conditions are promising for the application of A-TDCS as an adjunctive method in fluency therapy for adults who stutter. There has been very limited research using TDCS in developmental disorders of communication, likely due to an understandable caution regarding interacting with neuro-plastic processes during childhood. However, TDCS has an interesting potential for augmenting the limited therapeutic outcomes for adults living with persistent developmental difficulties. One study to date has addressed such a population. A-TDCS over visual cortex (area V5/MT) for 5 sessions combined with reading therapy improved reading speed and fluency in adults with developmental dyslexia, with benefits persisting one week after the intervention (Heth & Lavidor, 2015). However, the use of TDCS for adults with developmental disorders of speech has not yet been investigated.

It has been proposed that noninvasive brain stimulation to left IFC could increase speech fluency in developmental stuttering by supporting more stable activation of sensorimotor plans within oro-facial primary motor cortex (Neef et al., 2015b). In

addition, integration of sensory information to support speech may be improved by stimulating over this region. IFC could be effective either by supporting recruitment of brain circuits typically engaged in fluent speech, or by increasing the robustness of compensatory mechanisms for fluency.

1.5 Thesis scope

This thesis investigates how A-TDCS can be used to increase speech fluency, with a particular focus on the potential application in developmental stuttering. Evidence from studies of TDCS in motor and language skills suggests that speech motor function can be modified by A-TDCS. However, there are few studies directly testing how A-TDCS can affect speech, and it is not clear which stimulation parameters could yield the most beneficial effects.

The studies within this thesis focus on the application of A-TDCS over left IFC to enhance speech fluency. In chapter 2, I describe a series of experiments investigating the effects of a single session of A-TDCS over left IFC on the speech motor skills of people who do not stutter. We compared the effects of stimulation at different current intensities, and in uni-hemispheric versus bi-hemispheric configurations. These experiments aimed to inform the following studies in people who stutter. In chapter 3, I present a study investigating whether a single session of A-TDCS over left IFC can reduce stuttering. A-TDCS was combined with a behavioural task using one TFI technique: choral speech. Following this feasibility study, we went on to conduct a randomised controlled trial of A-TDCS over left IFC in a 5-day intervention, with adults who stutter. I present the trial in chapter 4. The intervention combined two TFI techniques with A-TDCS, or with sham stimulation, and outcomes were measured in terms of change in speech fluency and in the psychosocial impact of stuttering, at 1- and 5-week follow-up. Finally, in chapter 5, I discuss the findings of the studies presented here, and consider the implications for further work aiming to understand the mechanisms underlying speech fluency, and to enhance these mechanisms with TDCS.

Chapter 2

A single session of A-TDCS over left IFC

on speech motor learning

2.1 Summary

A-TDCS can enhance motor learning in non-speech domains. Here, I investigated how A-TDCS interacts with speech motor learning during nonword repetition training, with consolidation of learning, and with generalisation to repetition of untrained stimuli. Sixty participants received A-TDCS over left IFC during training in one session, and sham stimulation in a control session. My primary question was whether A-TDCS to the left IFC would improve speech motor learning. Participants received one of three stimulation protocols, to address two further questions: can learning be further improved by using higher stimulation intensity (1 mA vs 2 mA), or by inter-hemispheric inhibition (cathode over right IFC)?

There was an unexpected effect of prior training on performance, which interacted with the effects of interest. Only the data from the first session were retained for analysis, therefore, and the effects of stimulation were compared between subjects. I found that nonword repetition accuracy increased by the end of the training, in all conditions. However, the improvement was significantly greater under A-TDCS to the left IFC, compared with sham stimulation. Learning was retained in the hour following training, across all A-TDCS and sham groups, and further increased when measured the following day. However, A-TDCS did not increase these consolidation effects. There were no significant increases in learning of trained nonwords, or in the consolidation of this learning, when A-TDCS was applied at a higher intensity, or with the cathode over right IFC. Following training, learning generalised to untrained nonwords, in all conditions. This generalised learning was not increased by uni-hemispheric stimulation, at 1 mA or 2 mA intensity. Bi-hemispheric stimulation increased accuracy on untrained nonwords one hour following training, relative to

sham. However, this effect was due to a difference at pre-training baseline, which was non consistent with a true learning effect. In summary, I found that A-TDCS to left IFC has a specific effect on the learning, but not the consolidation, of speech motor skill.

2.2 Introduction

Speech production is a highly complex behaviour, taking years to achieve full mastery. Learning to speak involves acquiring the complex motor programmes for the movement of the articulators and vocal folds in precise temporal sequence, as well as associating these programmes with phonological forms and word meanings. The left IFC plays a key role in speech production, comprising regions involved in motor planning, and integration of auditory and somatosensory information (Guenther et al., 2006; Bohland et al., 2010). Learning, or re-learning, speech motor patterns to remediate a developmental or acquired speech disorder necessitates intensive support and practice. Investigating methods to support IFC function during speech training could inform therapeutic interventions.

2.2.1 A-TDCS improves motor learning

The general introduction (sections 1.3.2. and 1.3.3) summarised research findings demonstrating the therapeutic potential of A-TDCS as an adjunct to behavioural interventions. The behavioural effects of A-TDCS were first shown in the motor domain (Nitsche et al., 2003c; Boggio et al., 2006a). Studies investigating the effects of a single application of TDCS over M1, concurrent with a motor task, typically test for effects up to tens of minutes after the stimulation, and functional improvements persist at these intervals (Hummel et al., 2005a; Galea et al., 2009; Galea et al., 2011). Applied over multiple sessions TDCS can yield longer lasting behavioural improvements, which could have a clinical application. A recent consensus paper notes that despite considerable variation in effects, likely influenced by differences in experimental protocols, TDCS studies of motor learning have moderate effect sizes (Buch, 2016).

Effects on motor skill acquisition

Motor learning can be broadly divided into skill acquisition ('online' effects) and the consolidation of this learning, which may involve further 'offline' gains, or simply the retention of skill over time. Numerous studies have demonstrated that A-TDCS to contralateral M1, concurrent with motor training, can increase online learning (Nitsche et al., 2003c; Stagg et al., 2011a; Kantak, Mummidisetty & Stinear, 2012).

Effects on motor skill consolidation

Studies using a mutiple-session design show that A-TDCS also has a positive effect on motor skill consolidation (Reis et al., 2009; Reis et al., 2015). Reis and colleagues (Reis et al., 2009) found that 5 daily sessions of visuo-motor training combined with A-TDCS to left M1 resulted in measurable benefits lasting at least 3 months. A-TDCS promoted offline consolidation processes, but there was no significant increase of online learning across the training days. A follow-up study showed that the passage of time, rather than sleep, was important for the modulation of offline effects by A-TDCS (Reis et al., 2015).

It should be noted that multiple sessions of A-TDCS do not always result in a specific offline effect. Other studies have shown a dissociable effect on online learning (Prichard et al., 2014, Waters-Metenier et al., 2014), and Reis and colleagues (2009) found some online benefit of A-TDCS during the first training day. Although variations in task and protocol likely influence the behavioral outcome of A-TDCS applied during motor learning, both the acquisition and consolidation processes can be improved.

2.2.2 Effects of stimulation intensity and cathode position

Different stimulation protocols, for example varying electrode placement and current intensity, can differentially affect the outcomes of A-TDCS combined with behavioural training.

Uni-hemispheric vs bi-hemispheric stimulation protocols

A-TDCS studies typically employ a uni-hemispheric stimulation configuration, with the cathode over the contralateral SOR. However, a bi-hemispheric configuration, with the cathode over the homologous region in the opposite hemisphere, can be used where inter-hemispheric inhibition is hypothesized to be beneficial. For example, in aphasia, recruitment of the spared hemisphere can inhibit recovery of the affected hemisphere, so bi-hemispheric TDCS can promote a functional 're-balancing' (Lindenberg et al., 2010; Bolognini et al., 2011; Marangolo et al., 2016). Bi-hemispheric stimulation can also be effective in healthy participants (Williams, Pascual-Leone & Fregni, 2010; Waters-Metenier et al., 2014), and may have particular benefits for generalisation of learning (Waters-Metenier et al., 2014). However, results of studies directly comparing the effects of uni-hemispheric and bi-hemispheric configurations in healthy participants are equivocal. Two studies have found no significant difference between the effects of uni-hemispheric and bi-hemispheric stimulation of M1 (Prichard et al., 2014; Kang & Paik, 2011), whereas one study found that bi-hemispheric stimulation had a larger effect on motor learning (Vines et al., 2008).

Effect of increasing current intensity

TDCS is typically delivered with current intensity of 1 to 2mA in line with safety recommendations (Nitsche et al., 2003a; Poreisz et al., 2007; Fregni et al., 2015). There is an assumption that 2 mA will yield a stronger effect on cortical excitability, and on related behavior, which has led to clinical studies generally using 2 mA intensity. However, this assumption has limited evidence. In their early study, Nitsche and Paulus (2003) found increased excitability with increased intensity, comparing 0.2 with 1 mA. However, no excitability differences were seen in a comparison of 0.8, 1 and 1.2 mA in a more recent study (Kidgell et al., 2013). In the few studies that directly compared the effects of different current intensities on behavioural measures, a higher intensity yielded significant change relative to sham, where 1 mA did not (Cuypers et al., 2013; Boggio et al., 2006b), although the effects of the two intensities did not significantly differ from each other.

2.2.3 A-TDCS and speech motor learning

Modulation of expressive language has been investigated using A-TDCS, for example stimulation of left IFC has improved performance on picture naming (Holland et al., 2011), learning novel grammar (de Vries et al., 2010) and verbal fluency tasks (Cattaneo, Pisoni & Papagno, 2011). However, there have been few studies focusing on speech motor skills. Increasing the outcomes of speech motor therapies would be particularly valuable, as affecting long-term change in speech disorders is difficult by behavioural intervention alone (Blomgren, 2013). Although oro-facial M1 is a potential target for A-TDCS to promote speech motor function, targeting left IFC could benefit multiple processes involved in speech production.

Three studies have assessed the effects of A-TDCS over IFC on improving speech function (Fiori et al., 2014; Marangolo et al., 2011; Marangolo et al., 2013). The speech articulatory ability of a group of healthy participants was improved using 2 mA A-TDCS applied over left IFC during a complex speech task, although this effect did not persist one hour after the training (Fiori et al., 2014). Two studies tested the effect of A-TDCS over the IFC in the treatment of apraxia of speech, following stroke. A-TDCS was effective in uni-hemispheric (Marangolo et al., 2011), and in bi-hemispheric (Marangolo et al., 2013) configurations, however the relative therapeutic benefit of these configurations has not been directly compared.

2.2.4 Using nonword repetition to measure speech motor skill

Nonword repetition can be used as an index of speech motor ability. In a nonword repetition task, participants listen to a novel word, and repeat it immediately. The ability to immediately repeat a novel word is clearly important for learning that word, and subsequently producing it accurately (Gathercole, 2006). Nonword repetition has been associated to language learning via a shared reliance on maintenance of phonological information in short-term memory (Gathercole, 2006). Reduced nonword repetition ability in developmental language disorders is well-established (Bishop, North & Donlan, 1996; Conti-Ramsden, 2003; Edwards & Lahey, 1998; Weismer et al., 2000; Estes, Evans & Else-Quest, 2007; Gathercole & Baddeley, 1990; Watkins, Dronkers & Vargha-Khadem, 2002). However, speech motor skill also constrains both nonword repetition and word learning ability (Watkins et al., 2002; Sasisekaran & Weisberg, 2013; Sasisekaran et al., 2010). Individual differences in motor speech ability or learning new articulatory-motor sequences (Munson, 2001; Munson, Edwards & Beckman, 2005) and in oro-motor control (Krishnan et al., 2013)

can affect nonword repetition. Furthermore, differences in nonword repetition ability have been shown in developmental stuttering, a speech motor disorder. Children who stutter have reduced nonword repetition ability, in the absence of language learning impairment (Anderson, Wagovich & Hall, 2006). Nonword repetition difficulty in childhood predicts persistence of the disorder (Spencer & Weber-Fox, 2014), and adults who stutter also show reduced nonword repetition skills (Byrd, McGill & Usler, 2015).

2.2.5 Research questions

In this study, I investigated whether A-TDCS to the left IFC can increase learning during and following a single session of speech motor training using nonword repetition. I tested learning at the end of the training, and the consolidation of this learning 1 and 24 hours after training. I also assessed generalisation of learning following the training, by testing nonwords that were untrained. The study included three different experiments, each testing a protocol that applied A-TDCS over the left IFC, against a sham control. The protocols differed with regard to stimulation intensity and cathode placement, to address the following questions:

1) Does anodal stimulation to left IFC improve speech motor learning?

I compared the effects of training during A-TDCS to left IFC, to training alone (sham), across the experiments. I predicted that learning would be improved in all TDCS conditions relative to sham.

2) Does increasing stimulation intensity give larger learning benefits?

Here I compared the effects of training with A-TDCS at 1 mA versus 2 mA (both to left IFC, with cathode on right SOR). I predicted that 2 mA A-TDCS would promote larger increases in learning and consolidation than 1 mA A-TDCS.

3) Does inter-hemispheric inhibition give larger learning benefits?

I compared the effects of training during bi-hemispheric stimulation (anode on left IFC, cathode on right IFC) with training during uni-hemispheric stimulation (anode on left IFC, cathode on right SOR) both at 1 mA intensity. I predicted greater increases in learning and consolidation following bi-hemispheric stimulation.

2.3 Methods

2.3.1 Participants

Sixty healthy, right-handed, native English-speaking volunteers completed the study (25 males, mean age 22.6 years). Participants had normal (including corrected to normal) vision and normal hearing, and had no history of language or neurological disorder. They were assessed on nonword repetition ability using the nonword repetition subtest of the NEPSY (Korkman, 1998). Participants were divided into three experimental groups to test the three protocols: 1 mA A-TDCS over left IFC with cathode over right supra-orbital ridge (1 mA RSOR), 2 mA with cathode over right supra-orbital ridge (2 mA RSOR), and 1 mA with cathode over right IFC (1 mA RIFC). Details of participant demographics for each protocol are in table 1. Participants in the three experimental protocol groups did not differ in age, gender or NEPSY subtest score. The NRES Committee South Central Oxford C: (11/SC/0482) approved the study. Participants gave their written informed consent, as per the procedure approved by the ethics committee.

Table 1: Participant demographic information

	n	**Mean age years (SD)**	**NEPSY total score (max. 46) (SD)**	**male: female**
Exp 1: 1mA RSOR	20	22.3 (3.9)	42.5 (2.6)	9:11
Exp 2: 2mA RSOR	20	22.1(3.8)	41.5 (2.5)	6:14
Exp 3: 1mA RIFC	20	23.4 (6)	42.5 (2.2)	10:10

2.3.2 Nonword repetition task

Stimuli

To create the nonword stimuli, we used the Australian Research Council (ARC) database (Rastle, Harrington & Coltheart, 2002) to select a list of monosyllabic nonwords with low phonotactic probability in English, excluding any homophones. We then combined the syllables to produce 48 four-syllable nonwords, using each syllable only once. Some example nonwords are /va^{1}kwai^{2}nilp^{3}oy^{4}/, /kim^{1}skwo^{2}jube^{3}kril^{4}/ and /gwuk^{1}pilf^{2}glip^{3}tud^{4}/. The nonwords were randomly divided into four sets of 12. All nonwords were recorded by a female native English speaker, and spoken with primary stress on the second syllable. Allocation of a nonword set for training was pseudo-randomised, so that it was balanced across TDCS and sham conditions, and protocols.

Task

During the task, audio-recordings of the nonwords were presented using Presentation software (Neurobehavioral Systems) on a Dell PC via Sennheiser headphones, at comfortable listening level. At pre-training baseline, participants listened to 24 nonwords and repeated each nonword immediately following its presentation. A visual cue for the participant to attend to the upcoming stimulus was presented in each trial. Twenty minutes of repetition training commenced immediately following the baseline, consisting of 10 training blocks, with a 40 second break between each block. Twelve of the 24 nonwords presented at baseline were used in the training phase. In a training block, each of the 12 nonwords was presented in turn for immediate repetition. The order of nonwords within a block was randomised. Post-training measures were completed 1 hour and 24 hours

following training. At both post-training time points, the trained and untrained nonwords were presented in random order, and participants repeated each nonword once. Untrained nonwords (i.e. the 12 nonwords that were not used in the training) were presented at baseline and both post-training time points. The study had a within-subject design, so that each participant repeated this procedure with different nonword sets one week later. A-TDCS was delivered during training in one session, and sham TDCS in the other session. The order of sessions was counterbalanced across participants.

Task scoring

Accuracy on the task was calculated by summing the total number of syllables correctly repeated for each set of nonwords at each time point (a maximum of 48 syllables for each set of nonwords). A syllable was counted as correctly repeated if all constituent phonemes were accurately repeated, and the syllable was produced in the correct position within the four-syllable nonword in which it occurred.

2.3.3 Transcranial direct current stimulation

A DC-stimulator (neuroConn GBH) was used to deliver the TDCS via two 35-cm^2 saline-soaked electrodes, yielding current densities of 0.029 mA/cm2 (1 mA protocols) and 0.057 mA/cm^2 (2 mA protocol). For the 1 mA RSOR and 2 mA RSOR protocols, the anode was centred on FC5 according to the 10-10 international EEG placement system, in portrait orientation, and the cathode was positioned on the contralateral supraorbital ridge, in landscape orientation (see figure 2). For the 1 mA RIFC protocol, the anode was centred on FC5, and the cathode was centred on FC6. The experiment had a within-subjects design, participants received 20 minutes of A-

TDCS paired with a task in one session and sham TDCS in combination with the task in the other session. In the active A-TDCS session, stimulation was ramped up in the initial 15 seconds, then held constant. In the sham session, stimulation was ramped up to the same intensity as the corresponding A-TDCS protocol in that experiment, over 15 seconds. The current was held constant for 15 seconds, and then ramped down for 15 seconds. The A-TDCS and sham sessions were counterbalanced, and were separated by 1 week. To achieve blinding of both participant and researcher to TDCS condition, an additional researcher operated the DC-stimulator.

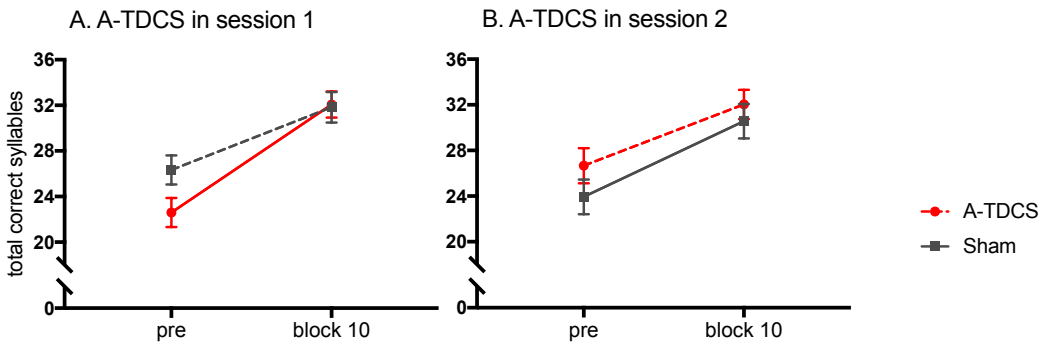
2.4 Results

2.4.1 Unexpected between-session carry-over effects

The main aim of the statistical analyses was to assess how TDCS affected speech motor learning. I expected the 1-week inter-session interval to be of sufficient duration to avoid carry-over effects of training or stimulation to subsequent repetition of novel nonword stimuli in the second session. However, during preliminary analyses a significant overall difference in performance was evident between the pre-training baselines for sessions 1 and 2 (mean session 1: 23.27 out of a possible 48 (SD: 6.64), mean session 2: 26.50 (SD: 7.67), t_{59} =-4.26, $p < .001$), suggesting carry-over effects which could confound our experimental manipulation.

A mixed-model ANOVA examined the effects of stimulation (A-TDCS, sham), time (pre vs. block 10) and experiment (Exp 1: 1 mA RSOR, Exp 2: 2 mA RSOR, Exp 3: 1mA RIFC) and included the nuisance between-subjects factor of session order (A-TDCS in session 1, A-TDCS in session 2). This analysis showed that session order significantly interacted with our effects of interest (two-way interaction between stimulation and session order, $F_{1,54} = 10.67$, $p = .002$; three-way interaction between stimulation, time and session order, $F_{1,54} = 10.29$, $p = .002$), and the effect of session order did not significantly differ among the three experiments (no significant interactions involving experiment). Figure 3 shows the three-way interaction involving session order averaged across the three experiments. Panel A shows nonword repetition accuracy at baseline and block 10, for all participants receiving A-TDCS in the first session (and sham in the second), and panel B shows accuracy for all participants receiving the stimulation conditions in the opposite order. For the group receiving A-TDCS first, the effects of stimulation and time significantly interacted ($F_{1,29} = 13.54$, $p = .001$),

and pre-training accuracy was significantly higher in the second (sham) session than the first ($t_{29} = -3.27$, $p = .003$). This indicated a significant difference in learning between the first and second session, as well as a significant carry-over of learning between sessions. For the group receiving sham first, there were significant effects of stimulation ($F_{1,29} = 7.11$, $p = .012$), and of training ($F_{1,29} = 10.41$, $p < .001$), but no interaction. This indicated learning was carried over between session 1 and 2, but learning within the two sessions did not significantly differ. Figures showing all data points for both sessions, in each experiment, are included for information in the appendix (fig. A1: experiment 1(1 mA RSOR); fig. A2: experiment 2 (2 mA RSOR); fig. A3: experiment 3 (1 mA RIFC)).



Panel A shows data averaged across the three experiments, for the groups receiving A-TDCS in session 1 and sham in session 2. Panel B shows data averaged across the three experiments, for the groups receiving sham in session 1 and A-TDCS in session 2. The mean total number of correctly repeated syllables in shown at baseline and at the end of training, for the A-TDCS (red)and sham (grey) sessions. Session 1 is shown as a solid line and session 2 as a dotted line. Error bars show the standard error of the mean (s.e.m.)

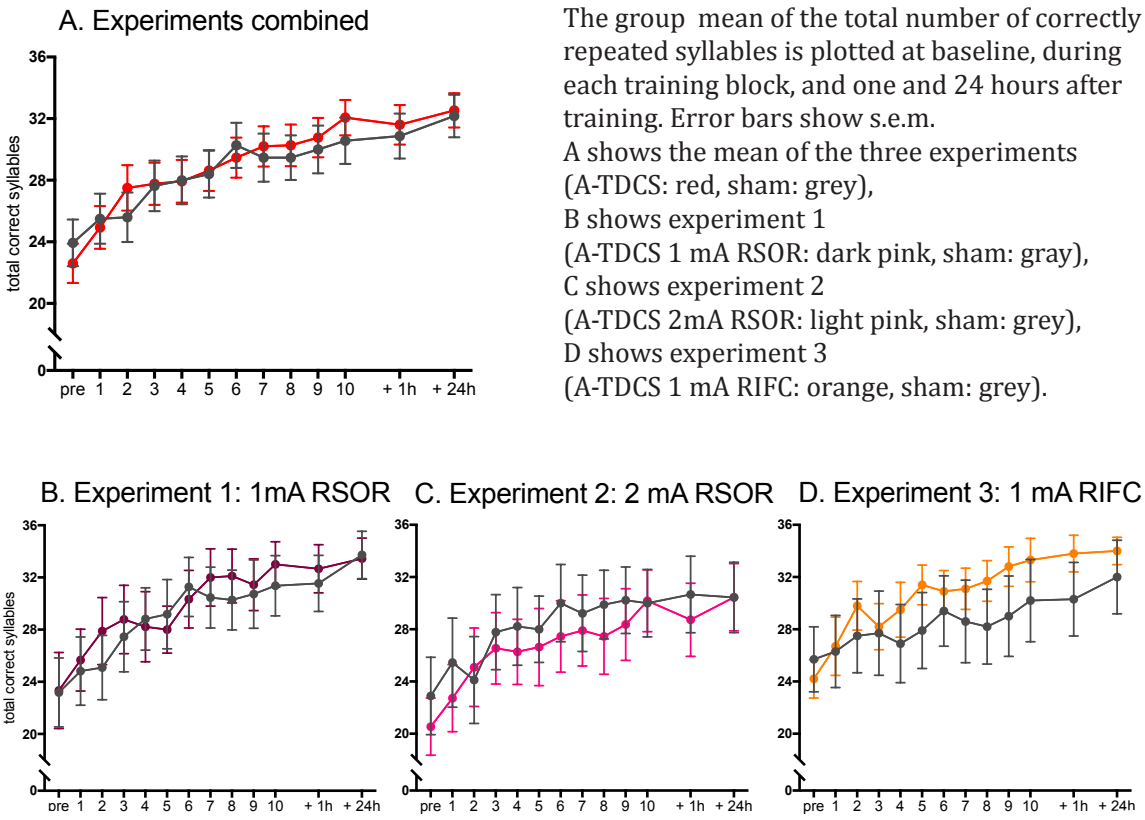
Figure 3: Confounding effect of session order on effects of interest (time, and the interaction of stimulation with time).

As the session order effect interacted significantly with the effects of interest, namely time and the interaction of time with stimulation condition, I focused the remaining

analyses on data from the first session only. (Our study design did not allow clear interpretation of the learning the effects in the second training session, in the context of prior training alone versus prior training combined with A-TDCS). In session 1, the A-TDCS group was compared with the sham group within each experiment, and the experiments were compared as specified by our research questions. In other words, stimulation became a between-subjects factor in all analyses.

2.4.2 Does A-TDCS over the left IFC improve speech motor learning?

Figure 4 shows nonword repetition accuracy during and following training, averaged across the three experiments (A), and separately for experiments 1(B), 2 (C) and 3 (D). I used separate analyses of these data to examine (i) the online learning effects, which were assessed by comparing the scores pre training with the scores at the end of training (block 10); (ii) consolidation of learning, which was assessed by comparing the change in performance from baseline at the end of training (block 10), 1 hour after training (+1 hour) and 24 hours after training (+24 hours).



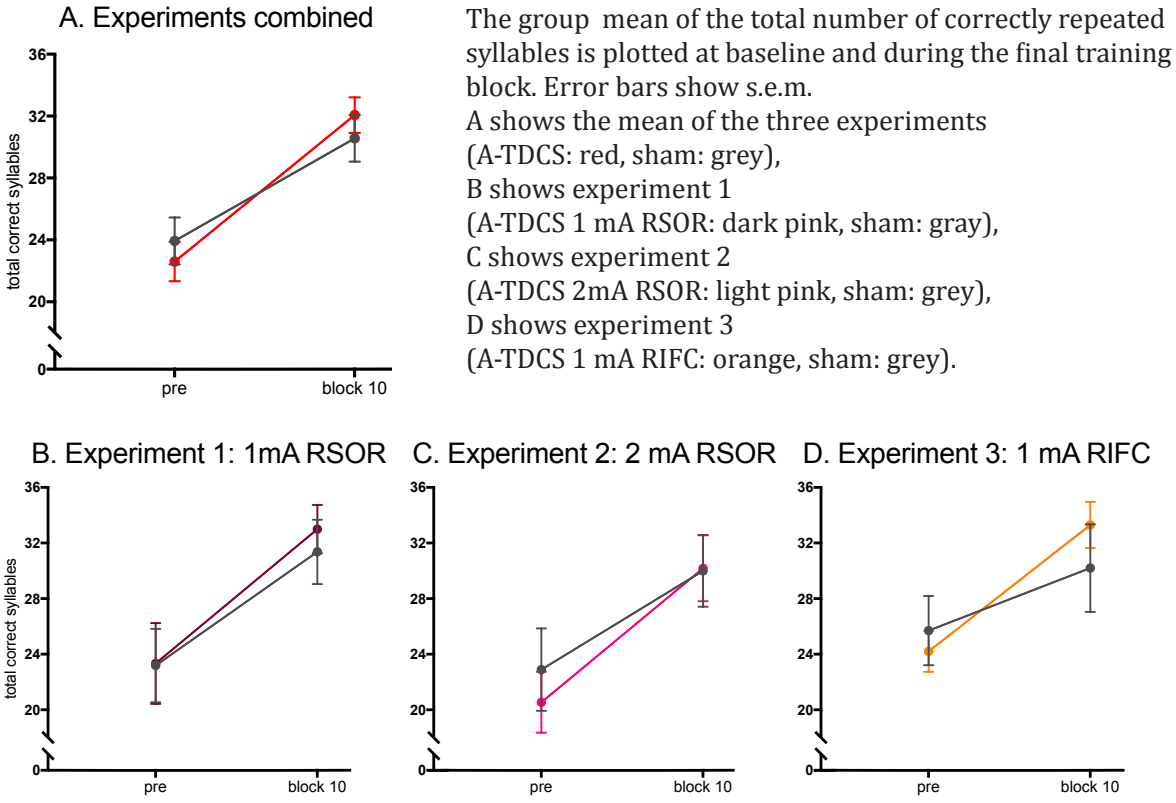
The group mean of the total number of correctly repeated syllables is plotted at baseline, during each training block, and one and 24 hours after training. Error bars show s.e.m.
A shows the mean of the three experiments (A-TDCS: red, sham: grey),
B shows experiment 1 (A-TDCS 1 mA RSOR: dark pink, sham: gray),
C shows experiment 2 (A-TDCS 2mA RSOR: light pink, sham: grey),
D shows experiment 3 (A-TDCS 1 mA RIFC: orange, sham: grey).

Figure 4: Repetition accuracy for trained nonwords at baseline, during training, and following training.

Online learning effects

Figure 5 shows the effects of training and A-TDCS (pre-training vs block 10) for the experiments combined (fig. 5A), and for each experiment separately (fig. 5 B to D). The effects of training were assessed using a mixed-model ANOVA on the total number of correct syllables, with stimulation condition (A-TDCS, sham) and experiment (Exp 1: 1 mA RSOR, Exp 2: 2 mA RSOR, Exp 3: 1mA RIFC) as the between-subjects factors, and time (pre, block 10) as a repeated measure. By the end of training, accuracy significantly improved across both stimulation groups, and all experiments (main effect of time: $F_{1,54} = 141.41$, $p < .001$), and A-TDCS significantly improved learning across all experiments (interaction between time and stimulation: $F_{1,54} = 4.51$, $p = .038$, fig 5A). The effects did not significantly differ among the three

experiments (no main effect of experiment, or any significant interaction involving experiment). However, I checked for an effect of A-TDCS in each experiment by running separate ANOVAs. This showed that the effect of A-TDCS did not reach significance in any one experiment, but was only revealed by the combination of experiments. Figure 5 (B-D) shows the online effects for each experiment.



The group mean of the total number of correctly repeated syllables is plotted at baseline and during the final training block. Error bars show s.e.m.
A shows the mean of the three experiments (A-TDCS: red, sham: grey),
B shows experiment 1 (A-TDCS 1 mA RSOR: dark pink, sham: gray),
C shows experiment 2 (A-TDCS 2mA RSOR: light pink, sham: grey),
D shows experiment 3 (A-TDCS 1 mA RIFC: orange, sham: grey).

Figure 5: Repetition accuracy for trained nonwords at baseline and final training block

Consolidation of learning

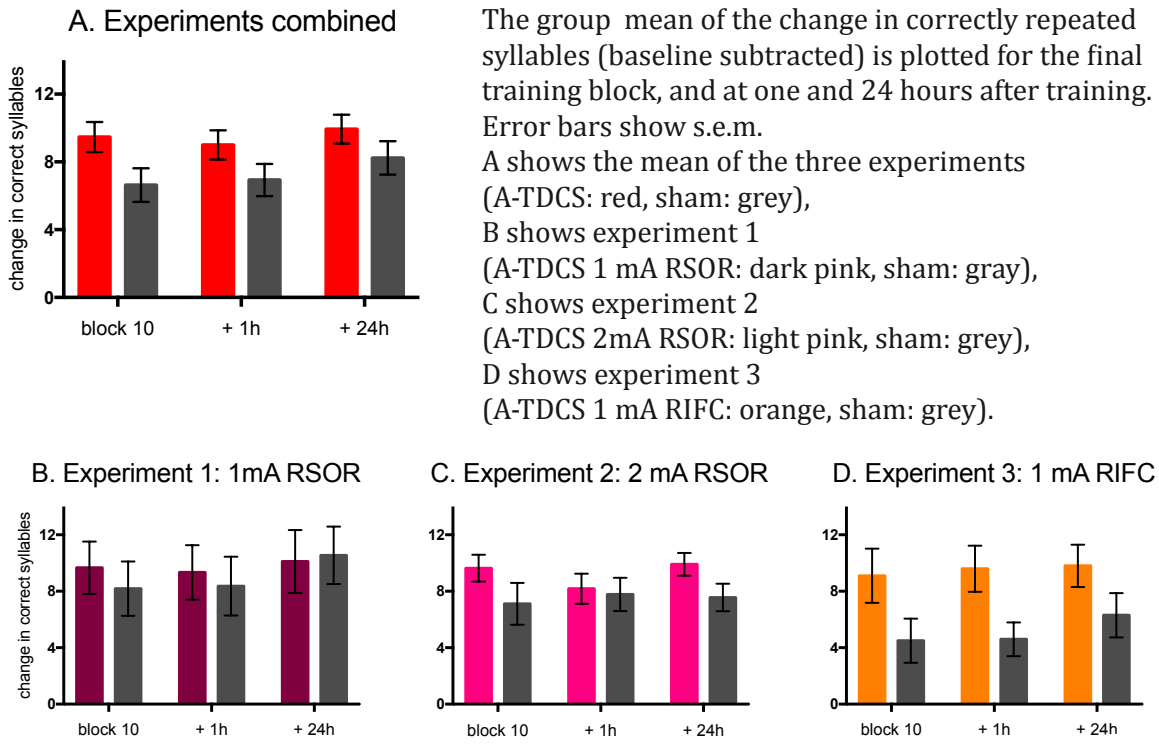
Figure 6 shows the change in accuracy, relative to baseline, at the end of training, and 1 and 24 hours after the training, for the experiments combined (fig. 6A), and for each experiment separately (fig. 6B to D). Consolidation of learning between the end of training and the post-training time points was tested using change scores (subtracting baseline performance) in a mixed model ANOVA, with stimulation

condition (A-TDCS, sham) and experiment (Exp 1: 1 mA RSOR, Exp 2: 2 mA RSOR, Exp 3: 1mA RIFC) as between-subjects factors and time (block 10, +1 hour, +24 hours) as a repeated measure. A main effect of time was revealed ($F_{2,108} = 4.00$, $p = .021$; fig 6A), which was followed up with separate ANOVAs, testing consolidation within-day (block 10, +1 hour) and overnight (+1 hour, +24 hours).

Within-day learning was retained but not further improved, in both stimulation groups, and across experiments (main effect of time $F_{1,54} < 1$, ns). Accuracy in the A-TDCS groups remained higher than in the sham groups, across experiments, but this effect only showed a trend towards significance (main effect of stimulation, $F_{1, 54} = 4.00$, $p = .051$). In the period including overnight, i.e. from 1 hour to 24 hours after training, both the A-TDCS and the sham groups showed further increases in accuracy, across experiments (main effect of time $F_{1,54} = 7.21$, $p = .010$), but the increase was not significantly greater in the A-TDCS relative to the sham groups (main effect of stimulation condition, $F_{1,54} = 2.53$, ns; no significant interactions involving stimulation condition).

The effects of training on offline learning did not significantly differ among the three experiments, in either the within-day or overnight intervals (no main effect of experiment, or interaction involving experiment). However, as for the online effects, I ran separate ANOVAs, to confirm a consistent pattern of offline consolidation across experiments (fig 6 B to D). All experiments showed retention of learning in the hour following training. However, there were some differences in the consolidation of learning overnight. In experiment 1, the increase in accuracy across the 1 mA RSOR and sham groups showed a trend towards significance (main effect of time, $F_{1,18} =$

4.36, p = .051), with no difference between the groups. No significant change in accuracy was evident in experiment 2, across the 2 mA RSOR and sham groups (main effect of time, $F_{1, 18} = 1.01$, ns), and again the groups were not significantly different. In experiment 3, learning was retained, rather than increased, in this time interval for both the 1mA RIFC and sham groups (main effect of time, $F_{1,18} = 2.70$, ns), and the A-TDCS group remained more accurate than the sham group (main effect of stimulation showed a trend towards significance, $F_{1,18} = 4.41$, p = = .050). On examination of figure panels B to D, the apparent differences in experiment 3 (i.e. the trend toward an effect of A-TDCS) seem to be driven by relatively poorer learning in the sham group. However, as noted above, there was no significant interaction between stimulation and experiment.



The group mean of the change in correctly repeated syllables (baseline subtracted) is plotted for the final training block, and at one and 24 hours after training. Error bars show s.e.m.
A shows the mean of the three experiments (A-TDCS: red, sham: grey),
B shows experiment 1 (A-TDCS 1 mA RSOR: dark pink, sham: gray),
C shows experiment 2 (A-TDCS 2mA RSOR: light pink, sham: grey),
D shows experiment 3 (A-TDCS 1 mA RIFC: orange, sham: grey).

Figure 6: Change in repetition accuracy for trained nonwords, at the end of training, and following training

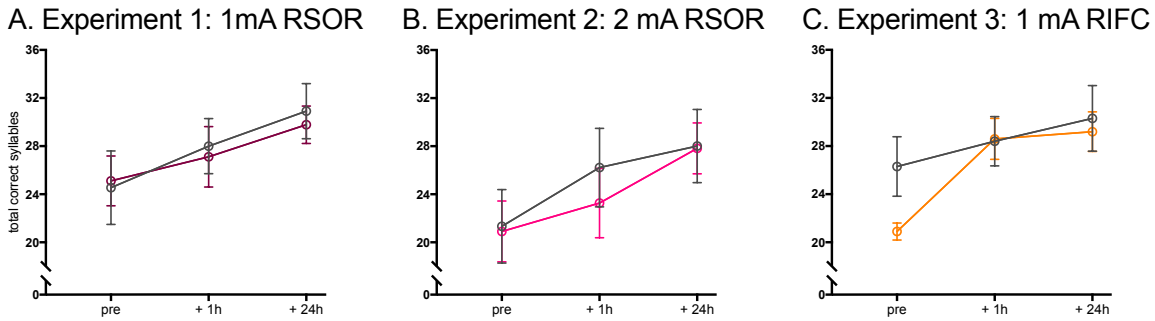
2.4.3 Generalisation of learning

Generalisation of learning was assessed with a mixed model ANOVA on the total number of correct syllables repeated for the untrained nonwords, with stimulation condition (A-TDCS, sham) and experiment (Exp 1: 1 mA RSOR, Exp 2: 2 mA RSOR, Exp 3: 1mA RIFC) as the between-subjects factors, and time (pre, + 1 hour, + 24 hours) as a repeated measure. The effects of the training on repetition of the untrained nonwords interacted differently with A-TDCS among the three experiments (interaction between experiment, stimulation condition and time: $F_{4,108} = 2.64$, $p = .038$). Figure 7 shows repetition accuracy on untrained nonwords, for experiments 1(A. 1 mA RSOR), 2 (B. 2 mA RSOR) and 3 (C. 1 mA RIFC).

Separate ANOVAs for each experiment revealed a consistent pattern across the two uni-hemispheric stimulation experiments. Accuracy increased over each time interval, across the A-TDCS and sham groups, indicating generalisation of learning in experiment 1 (main effect of time, $F_{2,36} = 10.56$, $p < .001$; pre to +1 hour $F_{1,18} = 4.58$, $p = .046$; +1 to +24 hour $F_{1,18} = 6.52$, $p = .020$) and experiment 2 (main effect of time, $F_{2,36} = 32.06$, $p < .001$; pre to +1 hour $F_{1,18} = 22.56$, $p < .001$; +1 to +24 hour $F_{1,18} = 13.70$, $p = .002$). However, A-TDCS did not increase the generalisation of learning, i.e. there was no significant main effect of stimulation condition, or interaction between stimulation condition and time, in either experiment.

In experiment 3, where 1 mA RIFC was compared with sham, the effect of A-TDCS interacted significantly with generalisation of learning (interaction between stimulation condition and time, $F_{2,36} = 4.27$, $p = .022$). Accuracy of repeating untrained nonwords increased for both the A-TDCS and sham groups 1 hour after the

training (main effect of time $F_{1,18} = 26.11$, $p < .001$) but this effect was larger for the A-TDCS group (interaction between stimulation condition and time $F_{1,18} = 8.53$, $p = .009$; figure 7C). This effect was driven by lower accuracy in the A-TDCS group than the sham group at baseline, however, rather than increased accuracy 1 hour post-training in the A-TDCS group, compared with sham. In fact, performance was equivalent in the two groups 1 hour post-training. To clarify interpretation of this effect, I also compared baseline accuracy on the untrained nonwords with the nonwords that were subsequently trained, within the A-TDCS group, using a paired t-test. I found that the untrained nonwords were repeated significantly less accurately at baseline than trained nonwords, in the A-TDCS group ($t_9 = 2.75$, $p = .023$). (Note that there was no difference in baseline performance between the trained and untrained nonwords in experiments 1 and 2). Finally, I tested generalisation in the interval between 1 hour and 24 hours after training in experiment 3, and found that learning was retained across the A-TDCS and sham groups, but not further improved (main effect of time $F_{1,18} = 1.61$, ns).



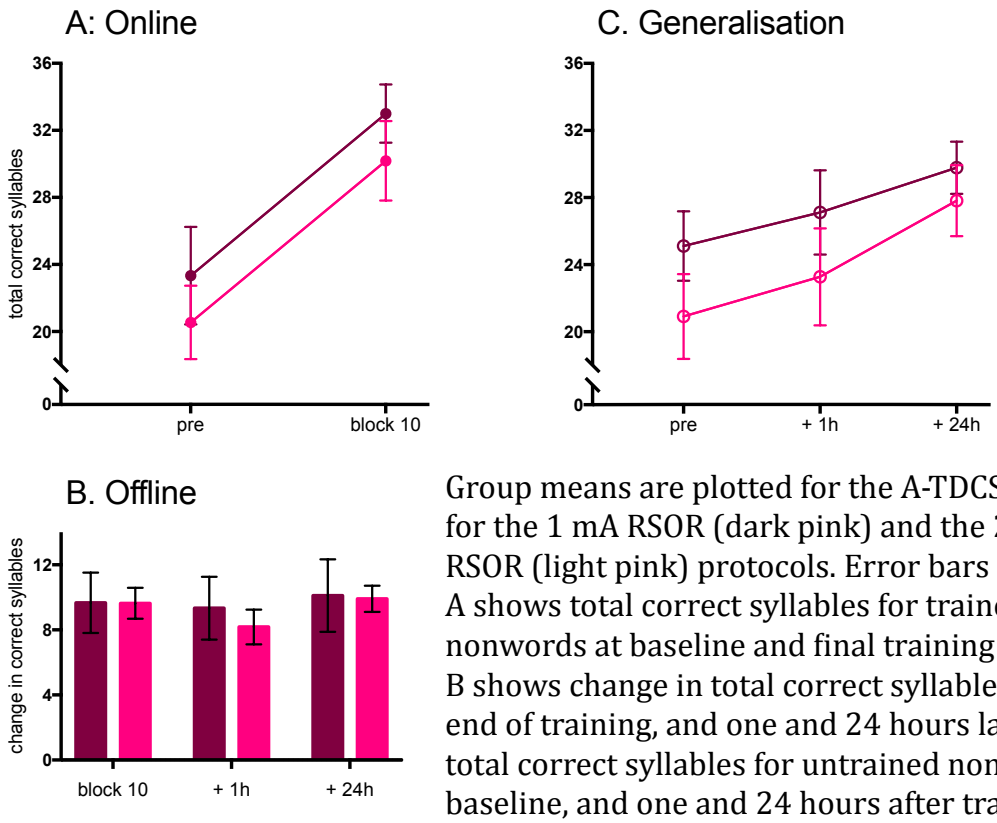
The group mean of the total number of correctly repeated syllables is plotted at baseline, and one and 24 hours following training. Error bars show s.e.m.
A shows experiment 1 (A-TDCS 1 mA RSOR: dark pink, sham: gray),
B shows experiment 2 (A-TDCS 2mA RSOR: light pink, sham: grey),
C shows experiment 3 (A-TDCS 1 mA RIFC: orange, sham: grey).

Figure 7: Repetition accuracy on untrained nonwords, at baseline and following training

2.4.4 Does increasing stimulation intensity give additional learning benefits?

The A-TDCS groups in experiment 1 (1 mA RSOR) and experiment 2 (2 mA RSOR) were directly compared to confirm the lack of a significant benefit of using a 2 mA intensity, suggested by the preceding analyses. Figure 8 shows the effects for each protocol for online learning (A), the consolidation of learning (B), and generalisation of learning (C). A mixed model ANOVA on total correct syllables, with time as a repeated measure (pre, block 10) and protocol (1mA RSOR, 2 mA RSOR) as a between groups factor showed no significant difference between protocols in online learning (no significant interaction between protocol and time). A mixed model ANOVA on change scores, with time as a repeated measure (block 10, +1 hour, + 24 hours) and protocol (1mA RSOR, 2 mA RSOR) as a between groups factor showed no significant difference between protocols on the consolidation of learning (no main effect of protocol, or interaction between protocol and time). A mixed model ANOVA on total correct syllables for the untrained nonwords, with time as a repeated measure (pre, +1 hour, + 24 hours) and protocol (1mA RSOR, 2 mA RSOR) as a between groups factor, confirmed that the protocols did not differ in effects (no main effect of protocol or significant interaction between protocol and time).

In summary, I found that increasing the stimulation intensity from 1 mA to 2 mA had no effect on online learning, offline consolidation or generalisation of learning.



Group means are plotted for the A-TDCS groups, for the 1 mA RSOR (dark pink) and the 2 mA RSOR (light pink) protocols. Error bars show s.e.m. A shows total correct syllables for trained nonwords at baseline and final training block. B shows change in total correct syllables at the end of training, and one and 24 hours later. C shows total correct syllables for untrained nonwords at baseline, and one and 24 hours after training.

Figure 8: Comparison of 1 mA RSOR and 2 mA RSOR protocols

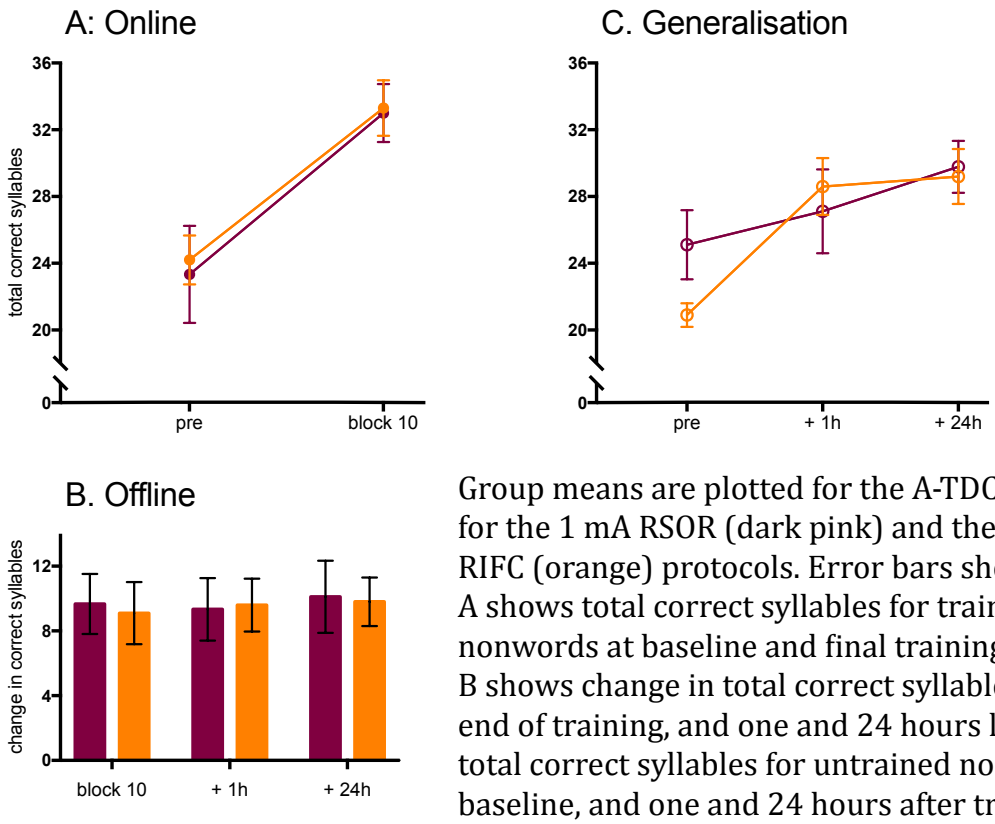
2.4.5 Does cathodal stimulation over right IFC give larger learning benefits?

The A-TDCS groups in experiment 1 (1 mA RSOR) and experiment 3 (1mA RIFC) were directly compared to test for significant benefits of using a bi-hemispheric configuration. Figure 9 shows the effects for each protocol for online learning (A), the consolidation of learning (B), and generalisation of learning (C). A mixed model ANOVA on total correct syllables, with time as a repeated measure (pre, block 10) and protocol (1mA RSOR, 1 mA RIFC) as a between groups factor showed no significant difference between protocols in online learning (no significant interaction between protocol and time). A mixed model ANOVA on change scores, with time as a repeated measure (block 10, +1 hour, + 24 hours) and protocol (1mA RSOR, 1 mA RIFC) as a between groups factor showed no significant difference between protocols

on the consolidation of learning (no main effect of protocol, or interaction between protocol and time).

A mixed model ANOVA on total correct syllables for the untrained nonword, with time as a repeated measure (pre, +1 hour, + 24 hours) and protocol (1mA RSOR, 1 mA RIFC) as a between groups factor, tested for differences in generalisation of learning. The protocols significantly differed in their effect on generalisation (interaction between protocol and time $F_{2,34} = 4.04$, $p = 0.27$). Accuracy on untrained nonwords improved more following 1 mA RIFC than the 1 mA RSOR, 1 hour after training (interaction between protocol and time $F_{1,17} = 6.96$, $p = .017$). Similarly to the apparent generalisation effect seen in the comparison if 1 mA RIFC with sham, this effect was driven by lower accuracy in the RIFC group than the RSOR group at baseline, rather than greater accuracy 1 hour post-training in the RIFC group. Across both the protocols, accuracy was retained, but did not further increase, in the following 24 hours (no significant main effect on time or interaction with protocol).

In summary, a 1 mA A-TDCS with cathode over RIFC did not increase online learning effects or, offline consolidation effect, relative to placing the cathode over RSOR. Untrained nonwords were repeated less accurately at baseline in the 1 mA RIFC group than the 1 mA RSOR group, but this difference was not evident 1 hour or 24 hours after training.



Group means are plotted for the A-TDCS groups, for the 1 mA RSOR (dark pink) and the 1 mA RIFC (orange) protocols. Error bars show s.e.m. A shows total correct syllables for trained nonwords at baseline and final training block. B shows change in total correct syllables at the end of training, and one and 24 hours later. C shows total correct syllables for untrained nonwords at baseline, and one and 24 hours after training.

Figure 9: Comparison of 1 mA RSOR and 1 mA RIFC protocols

2.5 Discussion

In this study, I investigated how A-TDCS applied over the left IFC during nonword training affects (i) the ability to accurately repeat trained nonwords at the end of training; (ii) the consolidation of this speech motor learning; and (iii) generalisation to repetition of untrained nonwords. I tested whether A-TDCS-modulated learning was greater when current intensity was increased, or when cathodal stimulation was applied simultaneously to the right IFC. I found a specific effect of A-TDCS on the acquisition of speech motor skill, which was unchanged by increased current intensity over the left IFC or by cathodal stimulation over the right IFC. Consolidation of learning was not modulated by A-TDCS relative to sham stimulation. Generalisation of learning was not affected by either of the uni-hemispheric stimulation protocols. However, 1 hour following bi-hemispheric stimulation, accuracy of repeating untrained nonwords significantly increased. It should be noted that baseline accuracy on the untrained nonwords in this condition was particularly low, and post-training accuracy was not different to the comparisons groups (i.e. the sham group in experiment 3, or the 1mA RSOR group). Furthermore, bi-hemispheric stimulation did not increase overnight generalisation.

2.5.1 A-TDCS over left IFC improves online but not offline speech motor learning

Concurrent application of A-TDCS over the left IFC during nonword repetition practice increased accuracy relative to sham stimulation at the end of training. There was a trend towards retention of this benefit 1 hour after the training, but performance did not differ from sham when tested 24 hours after training. The online effect of A-TDCS shown here is in line with single-session studies of non-speech

motor learning, and with the one previous study of articulatory training in typical adults (Fiori et al., 2014).

In the previous articulatory training study by Fiori and colleagues, the sham group showed no change in performance compared with baseline, and the A-TDCS group performance returned to baseline when tested 1 hour after training (Fiori et al., 2014). By contrast, in the current study, performance increased during the nonword repetition task for the A-TDCS and the sham groups, and this increase in motor skill persisted 1 hour following training. This difference is likely due to task methodology; the nonwords were repeated multiple times during training, promoting learning in all groups, compared to the Fiori study where the 'tongue-twister' stimuli were presented only once at each time point. It has been argued that, for A-TDCS effects to persist, A-TDCS-induced plasticity needs to interact with the plasticity promoted by the task itself (Reis et al., 2015). The nonword task increased speech motor skill during the training, and the benefit of A-TDCS on repetition accuracy, was maintained an hour following training. Although this effect did not reach statistical significance, it gives some indication of retention of learning. Reis and colleagues (2015) found that significant offline gains following A-TDCS in combination with motor training emerged when tested from 3 hours after training, but not as early as 15 minutes after training. It is possible that testing at 1 hour after training in the current study was not optimal for assessing these within-day offline gains (e.g. too early for a significant difference to emerge between the A-TDCS and sham groups).

The effects of A-TDCS on consolidation of learning have only been examined previously in multiple-session studies. I included a retest at 24 hours after the

training in this single-session study, to capture any early effects on consolidation. I found that that there were offline gains in learning in the overnight period in the sham and the A-TDCS groups, but A-TDCS did not modulate this improvement. Mutiple-session studies (Reis et al., 2009; Reis et al., 2015) have measured offline effects cumulatively over several overnight periods. When the sham and A-TDCS groups differ, the sham group tends to lose skill overnight while the A-TDCS group retains or increases skill. Interestingly, the overnight decrease in the sham groups in both studies by Reis and colleagues (Reis et al., 2009; Reis et al., 2015) is driven by changes from day 2 onwards. In the first overnight period, similarly to our study, skill improvement was seen for both the A-TDCS and sham groups. This suggests that further investigation of A-TDCS effects on the offline consolidation of speech motor skill should employ a mutiple-session design to properly address these changes.

2.5.2 Increasing stimulation intensity does not give additional learning benefits.

I found no significant benefit of using 2 mA current intensity relative to 1 mA. Previous studies comparing 1 mA with a higher stimulation intensity, found that only the higher intensity induced improvement compared to sham (Cuypers et al., 2013; Boggio et al., 2006b). However, direct comparison of the two intensities did not reveal significant differences, which is consistent with the findings of the current study. It is notable that these studies reported no significant difference from sham in the 1 mA group, where similar studies using 1 mA stimulation intensity have shown significant behavioural improvements in tasks of these types (Stagg et al., 2011a; Vannorsdall et al., 2012). The well-documented inter-individual variability in TDCS effects might explain this difference between studies (Horvath, Forte and Carter, 2015; Krause et al., 2014; Wiethoff et al., 2014). However, the 'dosage' of TDCS, i.e.

the combination of the duration and current intensity per cm^2 (current density), is a related, and likely a critical factor. The studies by Cuypers et al. (2013), and Boggio et al. (2006) demonstrated that stimulation at intensities exceeding 1 mA, in combination with the given electrode size and duration of application, resulted in an effective A-TDCS dosage for those tasks. It does not follow, however, that stimulating above 1 mA should always result in a more effective dosage.

The effects of noninvasive brain stimulation on motor learning are limited by homeostatic mechanisms that ensure neural stability during learning (Siebner et al., 2004; Lang et al., 2004; Stagg et al., 2011a; Amadi et al., 2015). Therefore, to be effective, TDCS should be applied at a dosage that increases excitability but does result in a homeostatic limiting response. For example, 13 minutes of A-TDCS applied at 1 mA increased excitability of M1, measured by motor-evoked potentials, but 26 minutes of A-TDCS at the same intensity reduced excitability. Furthermore, 1 mA A-TDCS to left pre-frontal cortex resulted in a significantly improved behavioural response relative to 2 mA applied for the same duration (Hoy et al., 2013). In our study the dosages resulting from a current intensity of 1 mA or 2 mA for a 20-minute duration had a similar effect on learning (although effects did not reach statistical significance in either protocol). A longer or shorter duration may have dissociated the effects of the two intensities. In fact, where improvement in learning differed between the groups, it was numerically larger for 1 mA RSOR group. One speculative reason could be that, when stimulation was applied at 2 mA, a homeostatic response began to limit the change in excitability.

2.5.3 Inter-hemispheric inhibition does not increase acquisition or consolidation of speech motor skills

I found no benefit of using a bi-hemispheric protocol over IFC to enhance speech motor learning or consolidation. Studies of hand motor training with healthy participants have also, more often than not, found no significant benefit of a bi-hemispheric protocol relative to a uni-hemispheric one (Kang et al., 2011; Vines et al., 2008; Prichard et al., 2014). It has been argued that the healthy brain may be robust to the inhibitory effects of cathodal stimulation (Galea et al., 2009; Vines et al., 2008). Our results are consistent with this view. Speech production is strongly left lateralised, and bi-hemispheric TDCS over IFC has supported language recovery in aphasic patients (Marangolo et al., 2013; Marangolo et al., 2016), in whom right hemisphere activity can be maladaptive. However, in neurologically intact adults the right, non-dominant, IFC is unlikely to interfere with effective speech function. It remains an open question whether the beneficial effects reported in neurologically intact participants from bi-hemispheric stimulation in previous studies, would have also been achieved using uni-hemispheric stimulation.

2.5.4 Does inter-hemispheric inhibition have a specific effect on generalisation of learning?

Repetition accuracy on untrained nonwords improved 1 hour and 24 hours after training. A-TDCS using uni-hemispheric protocols did not increase the generalisation of learning. However, there was a significant increase in accuracy in repeating untrained nonwords 1 hour after training combined with bi-hemispheric stimulation. The effects of bi-hemispheric stimulation during training have transferred to

untrained stimuli, in studies with healthy participants (Waters-Metenier et al., 2014) and with aphasic patients (Marangolo et al., 2013).

Generalisation is important for maximizing therapeutic benefits, so it is interesting that I found some indication of an effect on generalisation in the bi-hemispheric condition, consistent with these studies. However, there are strong reasons to interpret this finding with caution. Firstly, the difference in the A-TDCS 1 mA RIFC group, when compared with their matched sham group, and with the A-TDCS 1 mA RSOR group, was significantly lower accuracy on untrained nonwords at baseline, not significantly higher following training. In addition, within the A-TDCS 1 mA RIFC group, baseline accuracy for the untrained nonwords was significantly lower than for the nonwords that were subsequently trained. Therefore, it is not the case that this group was generally poorer at the task at baseline, and so could benefit more from training. Furthermore, this is not an effect of the particular nonwords used in the untrained sets, as each nonword set was counter-balanced across experiments, stimulation conditions, and training conditions. It seems that performance on the untrained nonwords at baseline in the 1mA RIFC A-TDCS group was particularly poor, and this difference can only be due to chance. Therefore, it is somewhat problematic to conclude that this is a true learning effect, rather than a chance baseline discrepancy.

2.5.5 Limitations and implications

The unexpected differences in learning between our training sessions resulted in some limitations to the study analysis and interpretation of results. Focussing on the data from the first session only, halved the size of our experimental samples and also

potentially further reduced the power to find significant effects of stimulation relative to sham, due to using between-subjects analysis. For example, the effects of TDCS on learning were evident only when data from the three stimulation protocols were pooled. Variability in inter- and intra-individual responsivity to TDCS effects has been highlighted (Horvath et al., 2015; Krause et al., 2014; Wiethoff et al., 2014). TDCS study designs should aim to reduce, or to include measures of, this variability. I chose a within-subjects design to reduce the effect of inter-individual variability. However, in retrospect, a between-subjects design with larger experimental groups would have been a more suitable approach, to test for differences relative to sham, and between our experimental protocols.

Our reduced sample size likely also increased the influence of random variability in performance and learning that were independent of the A-TDCS effects. For example, in section 2.6.4 I addressed the particularly poor baseline performance on the untrained nonwords in the active bi-hemispheric stimulation group. In addition, I found some differences in learning between the sham groups for each experiment. In particular the sham group in experiment 3 learned less well than the sham groups in experiments 1 and 2. Although there was no significant difference in training effects between the experiments, this sham group difference did have some effect on the comparisons with the active stimulation groups. There appeared to be a specific benefit to consolidation of 1 mA bi-hemispheric A-TDCS, i.e. a trend toward larger increases in repetition accuracy at 1 and 24 hours after training. However, when the bi-hemispheric protocol was directly compared with the group receiving uni-hemispheric A-TDCS, no such benefit on consolidation was revealed. I had expected

to avoid such group differences by using a within-subjects design, but found that for a learning study this design was problematic in itself, as discussed above.

Recent studies of motor learning have considered the speed-accuracy trade-off function, to discriminate real skill change from compensatory changes between these factors. Here, I considered only the change in accuracy over the period of acquisition and consolidation of skill, which is a somewhat limited index of speech motor skill. There were likely also gains in reaction time (reflecting improvements in motor planning) and in execution time, as speech motor skill was increased. It would be useful to re-examine the effects found here, by integrating information regarding speed and accuracy in a model similar to that used in studies of non-speech motor learning (Reis et al., 2009). However, such a model would need to be validated for use with the speech motor task used here, as the shape of the speed-accuracy trade-off function may differ.

I targeted the left IFC as a key region for speech production. The electrode was centred on FC5, which corresponds to Broca's region (BA44/45). For an average participant head size, in addition to covering the IFC, the electrode likely extended posteriorly to cover oro-facial M1, and inferiorly to cover part of the superior temporal cortex. I predicted a functionally specific effect of the combination of task and A-TDCS. However, excitability increase in any or all of the regions covered, in combination with the task, would plausibly increase performance. Therefore I cannot conclude definitively that the effects here were due to modulation of the left IFC. I would need to include measures of brain function (e.g. fMRI) or excitability (e.g.

motor evoked potentials from M1) to elucidate the neurophysiological effects of A-TDCS in this configuration.

In summary, this study showed a benefit to speech motor learning from the application of A-TDCS over left IFC. Using higher stimulation intensity, or applying cathodal stimulation simultaneously to right IFC, yielded no additional benefit to learning or consolidation. Generalisation of learning was not improved following stimulation with uni-hemispheric configurations. The improvement following bi-hemispheric stimulation was due to anomalous performance on untrained nonwords at baseline, and was not consistent with a true learning effect. I completed this study to inform the methodology for the further studies included in this thesis. Since I did not find convincing evidence of the benefits of increased stimulation intensity or inter-hemispheric inhibition, I used a 1 mA current intensity in a uni-hemispheric configuration in studies described in the following chapters.

Chapter 3

A single session of A-TDCS over left IFC in adults who stutter

3.1 Summary

In this chapter, I describe a study in which I investigated whether a single session of anodal TDCS (A-TDCS) to left IFC could improve fluency in adults who stutter. In separate sessions, I either applied 1 mA A-TDCS for 20 minutes, or sham stimulation, over the left IFC. During the stimulation period I used choral speech (that is, participants read in unison with another speaker) as a TFI method. Stuttering frequency during sentence reading, paragraph reading and conversation was measured at baseline and at two outcome time points: immediately after the stimulation period and 1 hour later. Stuttering was reduced significantly at both outcome time points for the sentence-reading task, presumably due to practice, but not during the paragraph reading or conversation tasks. None of the outcome measures were significantly modulated by A-TDCS. Although the results of this single-session study showed no significant TDCS-induced improvements in fluency, there were some indications of a small increase in fluency in the A-TDCS session. I discuss factors that I believe may have obscured the expected positive effects of A-TDCS on fluency, such as unexpected adaptation effects in the training task, and heterogeneity in our sample of people who stutter. Consideration of such factors informed the subsequent randomised controlled trial.

3.2 Introduction

3.2.1 Abnormalities of the IFC in developmental stuttering

The IFC is consistently highlighted as an affected region in developmental stuttering. Several meta-analyses of functional brain imaging describe over-activation of the right IFC as a neural marker of the disorder (Brown et al., 2005; Budde et al., 2014; Belyk et al., 2015). Under-activity in the left IFC has been revealed also in several functional imaging studies with people who stutter (Wu et al., 1995; French et al., 2011; Fox et al., 1996; Neumann et al., 2005; Watkins et al., 2008; Toyomura et al., 2011). Over-activity in the right IFC may compensate for a left hemisphere deficit (Braun et al., 1997; Preibisch et al., 2003). Watkins and colleagues showed that a portion of left IFC – the ventral premotor cortex - was underactive during speaking, and that the white matter underlying this region was disrupted (Watkins et al., 2008). They suggested that this structural deficit affects the integration of sensory and motor information for speech, and the execution of speech motor commands. This hypothesis is in accordance with the results of the first DTI study in developmental stuttering (Sommer et al., 2002) and subsequent studies, summarised in a recent meta-analysis (Neef et al., 2015a). White matter integrity is consistently reduced in developmental stuttering within the left superior longitudinal fasciculus, including part of the arcuate fasciculus. The affected tracts connect inferior frontal regions (including ventral pre-motor and motor cortex, and IFC pars opercularis (BA44)) with parietal (inferior parietal lobule, supramarginal and angular gyri), and temporal cortex (superior and middle temporal gyri).

Transcranial magnetic stimulation studies have shown that the excitability of oro-facial motor cortex is altered in adults who stutter relative to adults who are typically

fluent (Neef et al., 2011b; Neef et al., 2015b). Specifically, the excitability of the tongue motor cortex is enhanced in the left hemisphere during transitions between speech gestures in fluent speakers, but this left-lateralised enhancement of excitability is absent in adults who stutter (Neef et al., 2015b). The lack of left-lateralisation of motor activation in adults who stutter is consistent with less efficient communication between the left IFC and motor cortex affecting timely planning of motor sequences. This suggestion is further supported by findings using MEG to measure the timing of brain activity during single word reading, which showed that adults who stutter activate left motor cortex prior to left IFC, a reversal of the timing seen in fluent speakers (Salmelin et al., 2000). It has been proposed that noninvasive brain stimulation to left IFC could increase speech fluency in people who stutter by supporting more stable activation of sensorimotor plans within oro-facial primary motor cortex (Neef et al., 2015b).

3.2.2 Using A-TDCS to enhance fluency in developmental stuttering

The effect of TDCS on developmental disorders of speech, including developmental stuttering, has not been investigated to date. The use of TDCS as a therapeutic adjunct has particular relevance in stuttering, where maintenance of therapy gains is problematic (as discussed in the general introduction). Critically, the effects of TDCS on behaviour depend upon stimulation being administered in combination with some task that itself engages the targeted brain region in that behaviour. This combination of stimulation and task is key to the promotion of long-lasting behavioural effects (Reis & Fritsch, 2011). TDCS current flow is relatively non-focal, meaning that current is likely to disperse across the targeted region as well as other regions. However, when the target region is activated by a task during TDCS, ongoing

plasticity changes in this region can be reinforced by the neuromodulatory effect of TDCS (Bikson et al., 2013; Stagg et al., 2011b; Reis et al., 2015). Therefore, choice of behavioural task is an important consideration.

Fluency-shaping behavioural therapy for adults who stutter can reduce stuttering symptoms by explicit practice of new speech patterns, such as prolonging phonemes or producing gentle onsets to syllables (O'Brian et al., 2003; Webster, 1982; Boberg et al., 1994). Effective behavioural therapy has been associated with subsequent 'normalisation' of the speech network shown following a course of fluency therapy (De Nil et al., 2003a; Neumann et al., 2005). However, the benefits of these behavioural therapies do not persist without continued training and practice (Kell et al., 2009; Ward, 2006). In addition, there is often a cost to speech naturalness, particularly in the short-term (Metz, Schiavetti & Sacco, 1990; Onslow et al., 1992; Runyan, Bell & Prosek, 1990; Teshima et al., 2010). A potential concern related to using TDCS with adults who stutter is that disfluent or unnatural speech may be reinforced. To reduce this risk when using TDCS with a fluency-shaping therapy, stimulation would need to be applied at the end of a successful course of therapy, only when techniques were mastered.

An alternative approach is to combine TDCS with TFI to promote the plasticity associated with fluent speech production. Using this approach, there is no prerequisite for mastery of a behavioural technique, as the behavioural effect is immediate. We chose to use choral speech, which involves speaking in unison with another person and induces complete fluency in adults who stutter (Cherry et al., 1956; Kiefte & Armson, 2008; Kalinowski et al., 2003c; Saltuklaroglu et al., 2009). The

effects of choral speech, like other TFIs, are transient, and stuttering typically returns as soon as the second speaker's voice is withdrawn (Kalinowski et al., 2003c). Similarly to a successful course of behavioural therapy, choral speech can 'normalise' activation of left IFC, (Wu et al., 1995; Fox et al., 1996). However, compared to fluency therapy, it gives a relatively effortless, immediate fluency, and does not compromise speech naturalness.

3.2.3 Research questions

In the current study, we investigated the feasibility of a single session of A-TDCS over the left IFC to prolong the temporary fluency induced by choral speech in adults who stutter. We hypothesized that choral speech would induce a 'fluent mode' of speech and normalize functioning of the left IFC, and that application of A-TDCS over the left IFC during this state would promote plasticity associated with speech network activity during fluent speech, e.g. timely communication between left IFC and motor cortex of the articulators, or improved sensorimotor integration. Together these effects would prolong the duration of the 'fluent mode' resulting in measurable reductions in stuttering following the TFI intervention, for the TDCS session relative to the sham stimulation session. We predicted that the fluency enhancing effect of choral speech would not persist in the sham session, and that stuttering rates would return to baseline levels once the TFI was withdrawn.

3.3 Methods

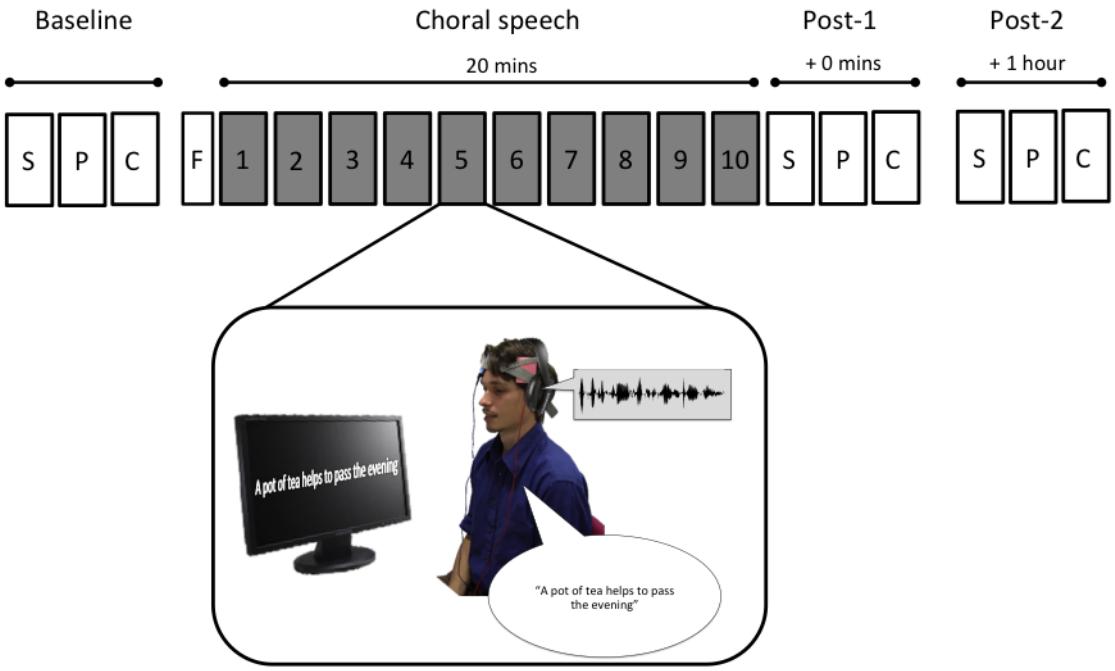
3.3.1 Participants

Sixteen right-handed native English speakers (2 female) took part in the study. All participants reported a diagnosis of developmental stuttering, which I confirmed, as a registered Speech and Language Therapist. The mean age of the participants was 30 years (range: 19-58 years). Participants had no history of any communication disorder or neurological impairment, other than developmental stuttering. All participants reported normal hearing and normal (or corrected-to-normal) vision. The Stuttering Severity Instrument, version 3 (SSI-3: Riley, 1994) was used as a standardized measure of stuttering symptoms. The average score across participants on the SSI-3 was 19.4, which is classified as mild (range: 7-28; borderline to moderate stuttering severity). The NRES Committee South Central Oxford C: (11/SC/0482) approved the study. Participants gave written informed consent, as per the procedure approved by the ethics committee.

3.3.2 Procedure

Each participant completed two experimental sessions that were separated by at least 1 and no more than 2 weeks. In each session, they read sentences out loud while listening to a recording of another person reading the same sentences. This choral speech practice lasted 20 minutes and was completed concurrently with A-TDCS in one session, and sham stimulation in the other. The order of the A-TDCS and sham sessions was counterbalanced across participants. Both the participant and I were blind to the stimulation conditions. In each session, speech fluency was assessed prior to the choral speech practice (baseline), immediately following the

practice (post-1) and again 1 hour later (post-2). Three fluency tasks were used: sentence reading, passage reading and conversation. Figure 10 illustrates the procedure for each session.



Speech assessment tasks were completed prior to the choral speech practice (baseline), immediately after choral speech practice (post-1) and one hour later (post-2). Three speech assessment tasks were complete at each time point: sentence reading (S), passage reading (P), and conversation (C). Half of the sentences from the sentence reading task were used in the choral speech practice. Following a brief familiarisation with the choral speech procedure (F), choral speech was practised for 20 minutes, in 10 blocks of 24 sentences.

Figure 10: Choral speech session

3.3.3 Transcranial direct current stimulation

A DC-stimulator (neuroConn GBH) was used to deliver the TDCS at 1 mA via two 35-cm^2 saline-soaked electrodes, yielding a current density of 0.029 mA/cm^2. The anode was centred on FC5 according to the 10-10 international EEG placement system, in portrait orientation, and the cathode was positioned on the contralateral supraorbital ridge, in landscape orientation (see figure 2 in general introduction). The experiment had a within-subjects design, participants received 20 minutes of A-TDCS paired with

a task in one session and sham TDCS in combination with the task in the other session. In the active A-TDCS session, stimulation was ramped up in the initial 15 seconds, and then held constant. In the sham session, stimulation was ramped up to 1 mA, over 15 seconds. The current was held constant for 15 seconds, and then ramped down for 15 seconds, at the start of the choral speech practice. To achieve blinding of both participant and I to TDCS condition, an additional researcher operated the DC-stimulator.

3.3.4 Choral speech practice

The sentences used for the choral speech practice and sentence reading task were taken from the Institute of Electrical and Electronics Engineers (IEEE) Harvard sentences (1969). Four sets of 24 sentences matched for number of syllables were compiled (each set had an average 10.3 syllables per sentence, and sentences ranged from 10-11 syllables). A female native speaker of British English made audio-recordings of two of the four sets; the other two sets were not recorded. The recordings were matched for duration (mean in ms (+/- SD), set 1: 2443 (226), set 2: 2468 (223)), and speech rate (mean syllables per second (+/- SD), set 1: 4.22 (0.33), set 2: 4.19 (0.35)). In each experimental session, one of the two recorded sets was randomly selected for use in the choral speech practice, and one matched unrecorded set was selected for use as the unpractised set in the sentence reading task. The set used in the choral speech practice was read aloud solo at baseline, read 10 times during choral speech practice, and read aloud solo again after the practice, at the two outcome time points. The matched unpractised set was read aloud solo, at baseline and after the choral speech practice, at the two outcome time points, as described in section 3.3.3 (and see fig. 10).

The choral speech practice consisted of 10 blocks. Within each block, the 24 sentences from one set were presented in a random order. Each sentence was displayed on a computer screen for 4.5 seconds, using Presentation software (Neurobehavioural Systems). The audio recording of the sentence started 1 second after the written sentence appeared. The participant was instructed to start reading the sentence when the audio recording commenced, and to attempt to speak in unison with the recorded voice. A practice run of four trials was used for familiarization. The familiarisation sentences were not repeated in the training stage.

3.3.5 Speech assessment tasks

At three time points, before the choral speech practice (baseline), immediately after (post-1) and 1 hour later (post-2), participants performed three speech assessment tasks in a fixed order (see fig. 10); these tasks were performed solo not in chorus. First, they read aloud two sets of 24 sentences from the IEEE (the one used for choral speech practice and a matched unpractised set, as described in section 3.3.4). Sentences from the two sets were presented in a random order. The sentences were displayed on a computer screen and the task was self-paced. Second, they read a passage aloud from a printed sheet, and no time constraint was given. Eight passages were used; they were taken from an intermediate 'English as a Foreign Language' online training resource (eslfast.com). Passages were matched for number of syllables (average 419, range 360 - 460). A novel passage was selected at random at each outcome time point. Finally, I initiated a brief conversation with the participant from a set of ten topics. A two-minute sample of conversation at each time point was used in the subsequent analysis (average of 335 syllables, range 163 - 633). Participants' speech during all tasks was recorded digitally for offline analysis.

3.3.6 Speech analysis and statistical analysis

I transcribed all audio-recorded speech samples, and counted stuttered syllables, and total syllables produced by the participant, for each sample. From this, I calculated the percentage of stuttered syllables (% ss). Stuttered syllables were defined as those containing repetitions of phonemes, prolongation of phonemes or 'blocks' (abnormal pauses, sometimes accompanied by audible tension). Other disfluencies, such as interjections or repetitions of multi-syllabic words or phrases, were not counted. I was blind to the experimental session when completing the transcriptions. Intra-rater reliability of stutter counts was determined by re-measuring a randomly selected sample of 10% of all recordings. Inter-rater reliability was similarly measured by comparing the stutter counts from a second researcher for a randomly selected sample of 10% of all recordings. A strong intra-class correlation was found for both the inter-rater (ICC = .97, $p < .001$) and intra-rater (ICC = .99, $p < .001$) measurements, indicating high reliability.

The data for all speech assessment tasks showed a significant positive skew, at most time points. Therefore, I used a logit transform to normalize the data and to allow use of parametric statistics in the analyses. I used the transformed data in all the analyses but I plotted the untransformed data in the graphs below for ease of understanding. I performed a 2 x 3 x 2 repeated measures ANOVA on the sentence reading task, with stimulation (A-TDCS, sham), time point (baseline, post-1, post-2) and sentence set (practised, unpractised) as within-subject factors, to test whether fluency increased (i.e. % ss decreased) following choral speech, and if A-TDCS modulated any improvement. I used simple planned contrasts to explore significant main effects of time point. When a significant interaction between time point and sentence set was

found, I carried out separate 2 x 2 repeated measures ANOVAs, with stimulation (A-TDCS, sham) and sentence set (practised, unpractised) as factors, at each time point.

I performed separate 2 x 3 repeated measures ANOVAs on the paragraph reading and conversation tasks, with stimulation (A-TDCS, sham) and time point (baseline, post-1, post-2) as within-subject factors, to test whether fluency increased following choral speech, and if TDCS modulated any improvement.

3.4 Results

All participants were completely fluent during choral speech. Fluency varied for some individuals between the two baseline sessions (see table 2), however there were no significant differences between A-TDCS and sham sessions in the logit transformed or raw % ss scores before stimulation and choral speech practice in any of the tasks. There was also a considerable range of % ss across participants (baseline sentence reading: 0 – 29 % ss, baseline passage reading; 0.2 - 22.8 % ss, baseline conversation: 1.1 - 11.7 % ss). A number of participants produced fluent speech (less than 1 % ss) during the baseline measures on one or more tasks in one experimental session. Five participants were fluent in one baseline session during sentence reading, and two of these participants were also fluent in one baseline session during passage reading. However, no participant was fluent on any task in both baseline sessions. For completeness, I present the results of analyses using data from all participants for the sentence and passage reading tasks, and the conversation task (see table 2), and also include the results of analyses with data excluded from participants who were fluent at baseline, where this revealed additional significant effects (see table 3: note that this table does not contain data for the conversation task, as no participants were fluent at baseline during this task). There is some limited evidence that women who stutter have a different pattern of symptoms to men (e.g. Silverman & Zimmer, 1979). However, the two female participants in our sample were not outliers at baseline, and excluding them from the analyses did not alter the results. Therefore, these data were included in all analyses.

Table 2: Raw and logit transformed % ss scores for all participants (N=16)

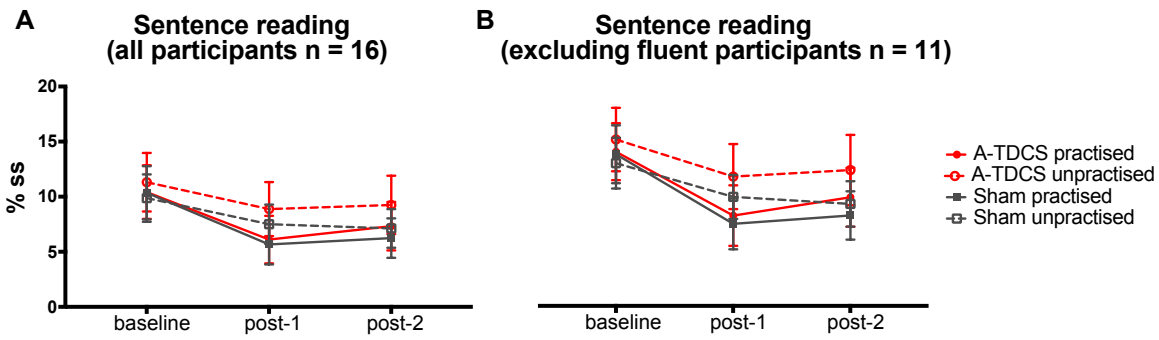
Fluency assessment task	A-TDCS session mean %ss (s.e.m.)						Sham session mean %ss (s.e.m.)					
	%ss			Logit transform			%ss			Logit transform		
	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2
Sentence Reading												
Practised sentences	10.42 (2.43)	6.11 (2.16)	7.33 (2.20)	-2.91 (0.45)	-3.92 (0.49)	-3.26 (0.35)	10.36 (2.41)	5.67 (1.82)	6.24 (1.79)	-2.80 (0.37)	-3.70 (0.41)	-3.48 (0.40)
Unpractised sentences	11.31 (2.65)	8.88 (2.45)	9.25 (2.65)	-2.60 (0.32)	-2.95 (0.34)	-2.94 (0.36)	9.88 (2.15)	7.50 (1.78)	7.12 (1.76)	-2.71 (0.32)	-3.08 (0.33)	-3.22 (0.40)
Passage Reading												
	10.45 (1.81)	9.45 (1.77)	9.03 (1.76)	-2.28 (0.26)	-2.56 (0.23)	-2.67 (0.26)	9.03 (1.75)	8.96 (1.79)	8.68 (1.54)	-2.74 (0.31)	-2.68 (0.25)	-2.72 (0.27)
Conversation												
	4.92 (0.72)	4.98 (0.86)	4.29 (0.65)	-3.14 (0.17)	-3.15 (0.17)	-3.31 (0.18)	4.62 (0.77)	4.58 (0.59)	4.53 (0.72)	-3.23 (0.17)	-3.17 (0.14)	-3.24 (0.17)

Table 3: Raw and logit transformed % ss scores excluding participants who were fluent at baseline for either the Sentence Reading task (N=11) or the Passage Reading (N=14).

Fluency assessment task	A-TDCS session mean %ss (s.e.m.)						Sham session mean %ss (s.e.m.)					
	%ss			Logit transform			%ss			Logit transform		
	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2	Baseline	Post-1	Post-2
Sentence Reading												
Practised sentences	14.60 (2.70)	8.55 (2.87)	10.29 (2.79)	-1.97 (0.25)	-3.07 (0.44)	-2.53 (0.31)	14.37 (2.74)	7.77 (2.41)	8.56 (2.29)	-2.03 (0.28)	-3.23 (0.54)	-2.83 (0.37)
Unpractised sentences	15.76 (3.01)	12.25 (3.08)	12.87 (3.33)	-1.88 (0.25)	-2.28 (0.29)	-2.20 (0.27)	13.52 (2.40)	10.32 (2.08)	9.66 (2.15)	-2.03 (0.23)	-2.40 (0.25)	-2.48 (0.24)
Passage Reading												
	11.80 (1.79)	10.57 (1.83)	10.15 (1.82)	-2.17 (0.19)	-2.33 (0.20)	-2.42 (0.22)	10.10 (1.82)	10.05 (1.87)	9.80 (1.54)	-2.45 (0.24)	-2.45 (0.20)	-2.43 (0.20)

3.4.1 Sentence reading task

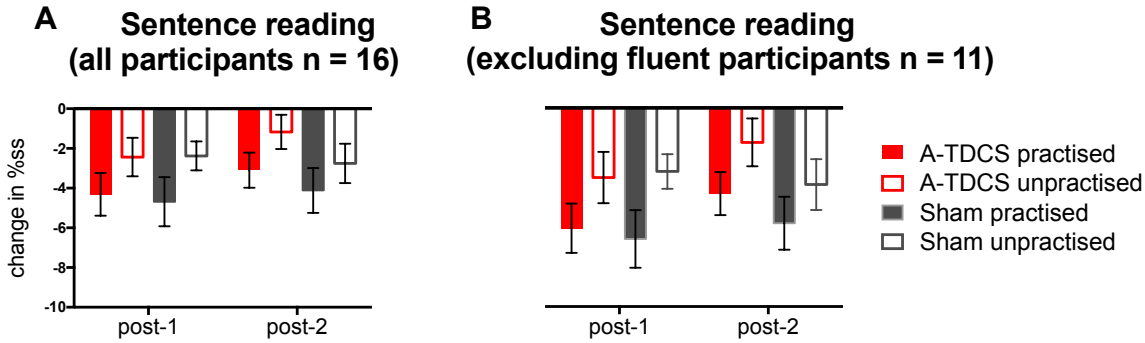
Mean raw and logit transformed % ss scores during the sentence reading task are presented in table 2 (all participants) and table 3 (excluding data from participants who were fluent during one session at baseline). When data from all participants were included in the analysis, the results showed that stuttering significantly reduced following the choral speech practice (main effect of time point: $F_{2,30} = 11.19$, $p < .001$); this effect was significant immediately after choral speech practice ($F_{1,15} = 11.41$, $p = .004$) and was maintained 1 hour later ($F_{1,15} = 15.34$, $p = .001$), when compared with baseline (Fig. 11A, Fig. 12A). The two outcome time points were not significantly different from each other. The choral speech practice significantly reduced stuttering more for the practised compared with the unpractised sentences (interaction between sentence set and time: $F_{2,30} = 3.51$, $p = .043$; Fig. 11A, Fig. 12A). Collapsed across all time points, the practised set was spoken more fluently than the unpractised (main effect of sentence set: $F_{1,15} = 22.44$, $p < .001$). Analysing each time point separately, there was no significant difference between the sentence sets at baseline. The interaction was due to significantly less stuttering for practised compared with unpractised sentences at the first outcome time point (post-1: $F_{1,15} = 13.63$, $p = .002$) but this difference was no longer significant 1 hour later (post-2: $F_{1,15} = 3.66$, $p = .075$). Importantly, these effects were not modulated by A-TDCS (there was no main effect of stimulation, or any significant interactions involving stimulation session).



% ss scores during sentence reading are plotted before choral speech practice (baseline), immediately following choral speech (post-1) and one hour following choral speech (post-2) for all 16 participants (A), and for the 11 participants who produced at least 1 % ss in both baseline sessions (B). A-TDCS is shown in red and sham is shown in grey. Solid lines are practised sets, and dashed lines are unpractised. Error bars show s.e.m. See text for significant main effects and interactions.

Figure 11: % ss during sentence reading

Re-analysis excluding data from the five participants who were fluent during one of the two baseline sessions revealed a very similar pattern of results, with significant differences as reported for the complete data set. For this analysis, however, the difference between practised and unpractised sentence was significant at both outcome time points ($F_{1,10} = 12.45$, $p = .005$: Fig. 11B, Fig. 12B).

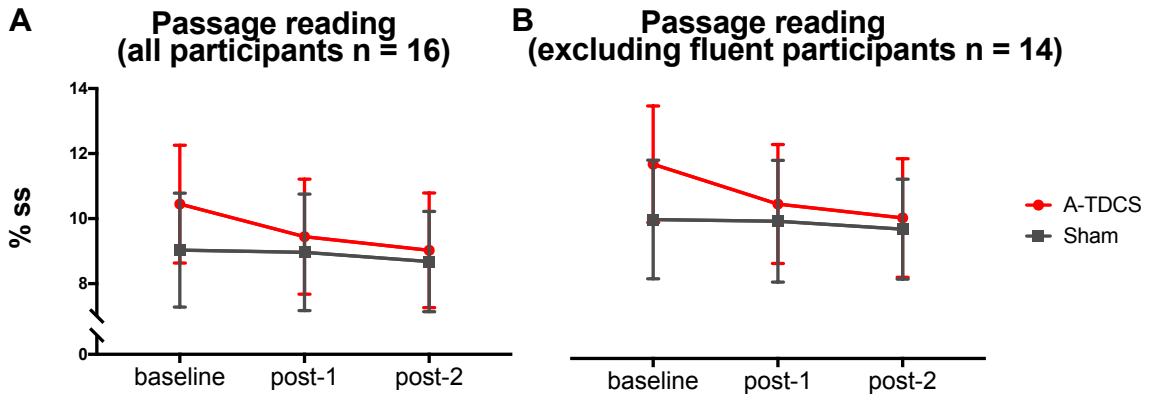


Changes in % ss scores from baseline during sentence reading (i.e baseline subtracted) are plotted immediately following choral speech (post-1) and one hour following choral speech (post-2) for all 16 participants (A), and for the 11 participants who produced at least 1 % ss in both baseline sessions (B).
Bars show the group mean for the two sentence types (filled - practised, unfilled - unpractised) and the two sessions (red - A-TDCS, grey - sham). Error bars show s.e.m.

Figure 12: Changes in % ss during sentence reading

3.4.2 Passage reading task

Mean raw and logit transformed % ss scores during the passage reading task are presented in table 2 (all participants) and table 3 (excluding data from participants who were fluent during one of the baseline sessions). When data from all participants were included in the analysis, results showed that there was no significant reduction in stuttering during passage reading following choral speech practice (no main effect of time point). Stuttering did not differ overall between the A-TDCS and sham sessions (no main effect of stimulation session) and A-TDCS did not modulate any effects (no significant interaction between time point and stimulation session; fig. 13A, fig. 14A).

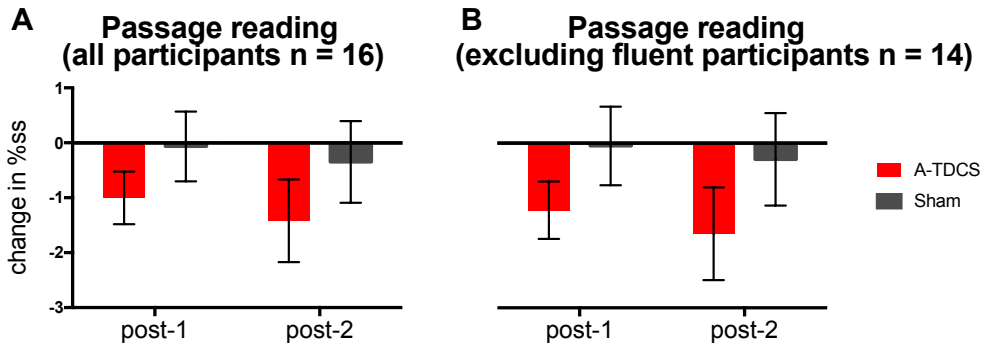


% ss scores during passage reading are plotted before choral speech practice (baseline), immediately following choral speech (post-1) and one hour following choral speech (post-2) for all 16 participants (A), and for the 14 participants who produced at least 1 % ss in both baseline sessions (B). A-TDCS is shown in red and sham is shown in grey. Error bars show s.e.m.

Figure 13: % ss during passage reading

A second analysis of the data, which excluded participants who were fluent during one baseline session, also did not reveal any significant effects (fig. 13B, fig. 14B). However, although the sessions were not significantly different, examination of the means (figs. 13 and 14, table 3) revealed that there was a greater reduction in

stuttering in the A-TDCS session compared to the sham session at both outcome time points and for both the full data set and the reduced data set. For the A-TDCS session, the absolute reductions of 1 and 1.4 % ss at post-1 and post-2 respectively represent relative decreases of 10% and 14% of the baseline stuttering rate. In contrast, for the sham session, the reductions were less than 0.5 % ss and represent decreases of 1% and 4% (post-1 and post-2, respectively) of the baseline.



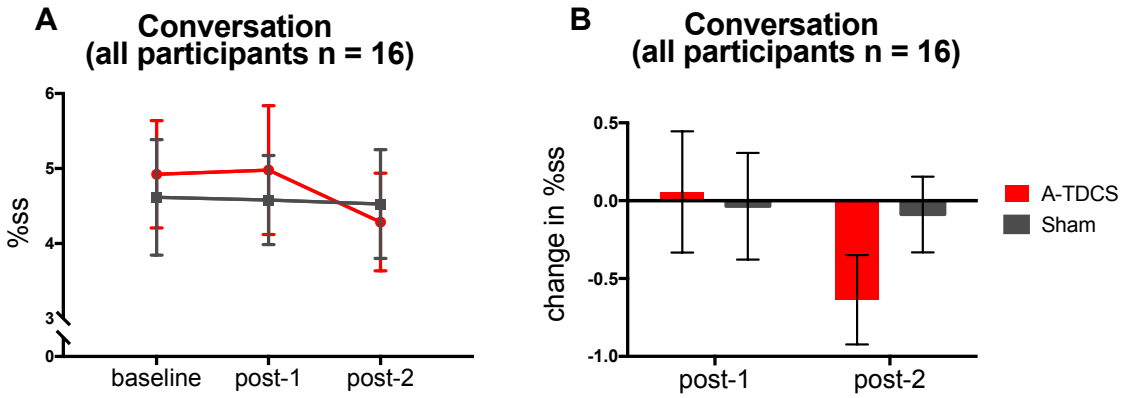
Changes in % ss scores from baseline during passage reading (i.e. baseline score subtracted) are plotted immediately following choral speech (post-1) and one hour following choral speech (post-2) for all 16 participants (A) and for the 14 participants who produced at least 1 % ss in both baseline sessions (B). Bars show the group mean for the session (red - A-TDCS, grey - sham). Error bars show s.e.m.

Figure 14: Changes in % ss during passage reading

3.4.3 Conversation task

Mean raw and logit transformed % ss scores during the conversation task are presented in table 2 (no participants were fluent at baseline on this task). There was no significant reduction in stuttering during passage reading following choral speech practice (no main effect of time point). Stuttering did not differ overall between the A-TDCS and sham sessions (no main effect of stimulation session) and A-TDCS did

not modulate any effects of choral speech (no significant interaction between time point and stimulation session, figs. 15A and B). As for the passage reading, although difference between sessions was not significant, examination of the means (figs. 15A and B, table 2) revealed that there was a greater reduction in stuttering following A-TDCS compared to sham stimulation at 1 hour after the practice. For the A-TDCS session, an absolute reduction of 0.63 in % ss represents a 13% decrease of the baseline stuttering rate. In contrast, for the sham session, the reduction was less than 0.1 % ss, representing a 2 % decrease of the baseline.



Panel A shows % ss scores during conversation before choral speech (baseline), immediately following choral speech (post-1) and one hour following choral speech (post-2) for all 16 participants. Panel B shows change in % ss scores during conversation immediately following choral speech (post-1) and one hour following choral speech (post-2) for all16 participants. No participants were fluent at baseline in this task. Red - A-TDCS, grey - sham. Error bars show s.e.m.

Figure 15: % ss and change in % ss during conversation

3.4.4 Other measures of speech fluency

Further analyses of other speech measures, such as stuttering rate (the number of stuttered syllables produced per minute) and speaking rate (the total number of syllables produced per minute) showed the same pattern of results as seen for the analysis of % ss.

3.5 Discussion

In this study, I investigated whether a single session of A-TDCS to the left IFC could enhance fluency in adults who stutter. I temporarily induced fluency during stimulation using choral speech. I hypothesised that when fluent speech was induced and combined with A-TDCS, some reduction in stuttering would be maintained once the choral speech was withdrawn. As expected, choral speech successfully induced complete fluency in all participants while they received either A-TDCS or sham stimulation. Speech fluency on sentence reading improved for at least 1 hour after the practice ended, but the effect was not significantly modulated by A-TDCS. For paragraph reading and conversation following A-TDCS, speech fluency improved slightly relative to the baseline assessments, but these changes were not significant when compared with the sham session. Below, I discuss the results in detail, the lessons learned from this feasibility study, and future directions.

3.5.1 Effects on sentence reading

I found a significant reduction in stuttering during sentence reading following the choral speech practice, in both the A-TDCS and sham sessions. The stuttering reduction was greater for the sentences that had been used during choral speech practice than for the unpractised sentences. Initially, this result appeared inconsistent with claims based on previous research that describe a lack of persistence in the fluency inducing effects of choral speech (Kalinowski et al., 2003c). However, it is likely that the fluency increase observed in the current study following choral speech was induced by the 10 repetitions of the sentences during the practice, rather than the presence of a second voice. Repetition adaptation has been demonstrated previously in people who stutter (Review in Bloodstein, 2008; Max &

Baldwin, 2010), and can persist for at least 24 hours. Consistent with the findings of the current study, a previous study (Max et al., 2010) reported that the adaptation effect generalises to novel sentences when these were randomly presented within the same passage of text, but the effect was smaller than that seen for repeated items. I did not find support for our prediction that combining A-TDCS with choral speech would result in a greater stuttering reduction relative to the reduction seen in the sham session. I found no significant difference between the A-TDCS and sham sessions in the size of the reduction in stuttering during sentence reading following choral speech practice. It is possible that any additional effect of A-TDCS on stuttering was masked by the repetition adaptation effect during sentence reading.

3.5.2 Generalisation of effects: passage reading and conversation tasks

I was also interested in whether the effects of A-TDCS on fluency might generalise to novel speech tasks not used during the choral speech practice. In the sham session, the size of the reduction in stuttering during passage reading or conversation was negligible. In the A-TDCS session, there was a larger reduction in stuttering during passage reading and conversation following choral speech but the size of this effect did not differ significantly relative to the sham session (see figs. 14A, 14B, and 15B). I suggest that this lack of statistical significance was influenced by two sources of variability: inter-individual variability in the response to A-TDCS, and both inter- and intra-individual variability in stuttering rates.

3.5.3 Sources of variability

Variability in TDCS effects

It is well known that the response to TDCS shows considerable variation among individuals. For example, A-TDCS to primary motor cortex produces facilitation of cortico-spinal excitability in only approximately three-quarters of young, healthy participants (Wiethoff et al., 2014). Some of the variability seen in the current study may be a consequence of inter-individual variations in the induced current flow and in responsivity to this current. Although TDCS is often used to induce changes in the cortex directly underlying the target electrode, the induced currents are complex, and are influenced by individual brain morphology (Bestmann, de Berker & Bonaiuto, 2015). Variability is seen in the behavioural, as well as the physiological, response to TDCS and the relationship between effects at these different levels is not well understood. Future TDCS studies with people who stutter might benefit from an individualised approach, for example, by tailoring electrode placement and stimulation intensity to each participant. For this approach, a dependent measure such as cortical excitability might be useful.

Variability in adults who stutter

A second source of variability in the current study was the inter- and intra-individual variability in stuttering symptoms, which is characteristic of this speech disorder (Soderberg, 1962; Karimi et al., 2013; Yaruss, 1997). Stuttering moments are intermittent, and their severity can vary considerably across time and contexts. I used both reading and conversation samples, in order to gain a representative view of stuttering symptoms. On average, the participants were more fluent in conversation than in the reading tasks, although four participants showed the

opposite pattern; so, the group was heterogeneous in this regard. In addition, participants varied in overall stuttering severity, and a number of participants who had milder symptoms produced fluent speech during some of the baseline speech assessment tasks. Excluding these participants from analysis yielded a numerically larger reduction in stuttering on passage reading in the A-TDCS session compared to the sham session (which showed negligible change), but this difference remained non-significant. This suggests that in order to assess the therapeutic potential of brain stimulation to treat fluency disorders, future studies would benefit from using a more homogeneous sample of people and those with more severe stuttering symptoms, thereby increasing the sensitivity to detect the beneficial effects of TDCS. This does pose some challenges, however, as there is a positive skew in severity in the wider population of people who stutter, with more people having a mild rather than a moderate or severe stuttering severity, at least when measuring core stuttering symptoms (Soderberg, 1962; Wingate, 2002; Jones et al., 2006). Once a therapeutic benefit has been demonstrated in a population of people with at least a moderate severity of stuttering, we can determine the parameters of stimulation that would be effective in the sizeable portion of the population with mild or very mild stuttering severity.

In addition, two of the 16 participants were female. Stuttering affects around four times more men than women, due to increased recovery rates in girls during childhood (Yairi et al., 1999). There is some, limited, evidence that women have a different pattern of stuttering symptoms to men (e.g. Silverman et al., 1979). Furthermore, there can be sex differences in responsivity to TDCS (Krause et al., 2014). Therefore, although excluding the female participants from analysis did not

affect the pattern of the results here, it may be advisable to ascertain efficacy of TDCS as a therapy adjunct in males who stutter first, before applying the approach also to women.

3.5.4 Measuring stuttering

The difference in fluency in conversation and reading tasks across participants highlights another consideration. In this study I measured only core, or primary, stuttering behaviours (Guitar, 2014; Ward, 2008). However, stuttered speech often includes secondary behaviours such as interjections ("um" "err"), repetitions of larger sections of speech (whole phrases), or phrase revisions (Guitar, 2014; Ward, 2008). These characteristics can indicate, in the case of a person who stutters, the avoidance of parts of speech that the speaker predicts may cause a stuttered moment. Such speech strategies occur more commonly during spontaneous speech than during reading and may explain why I found lower levels of stuttering in the conversation task relative to the reading tasks in this study. I included both tasks because reading tasks are more sensitive to stuttering in those adults who stutter who use avoidance to reduce stuttering symptoms, and conversation is the more ecologically valid measure. However, I believe that sensitivity to changes in speech fluency might be improved by measuring both primary stuttering symptoms, and other disfluencies, that could indicate avoidance, and have a negative impact on fluency. An effect of TDCS on core or secondary stuttering characteristics, or both, would be a positive outcome.

A consequence of the intra-individual variation in stuttering was a considerable difference in mean level of stuttering at baseline between the two sessions for the

passage reading and conversation tasks. I chose a within-participant design for the study. However, I failed to benefit from the greater sensitivity normally achieved by this design because of the large within-participant variability in baseline stuttering rates. Since the effects of a single session of TDCS are typically small, variance in baseline stuttering is particularly problematic.

3.5.5 TDCS did not increase stuttering

One of the aims of this single-session feasibility study was to rule out the possibility that the application of A-TDCS during speaking might decrease fluency in adults who stutter, either during or following the stimulation. The results do not indicate that our TDCS protocol had a detrimental effect on speech fluency, which was important to establish before continuing with mutiple-session studies. Furthermore, the small reductions seen here following choral speech in a single TDCS session (a decrease of around 1.5% stuttered syllables in passage reading) are clinically relevant, considering that a moderate to severe level of stuttering is 15-20% stuttered syllables (Onslow, 2000). This indicates the potential for TDCS to reduce stuttering, and that further research utilising multiple stimulation sessions could result in a significant positive effect on fluency.

3.5.6 Choral speech was an effective TFI

I chose to combine TDCS with choral speech, as I aimed to reinforce fluent speech, and choral speech induces fluency immediately and more successfully and to a greater extent than other methods (Saltuklaroglu et al., 2009). I found that choral speech had a complete and immediate fluency enhancing effect in all participants, in line with previous research. This indicates that choral speech is a useful behavioural

task for further studies of the effect of TDCS in adults who stutter. However, choral speech does have some limitations with regard to ecological validity, as it can only be used in reading tasks. Alternative approaches such as altering sensory feedback, or providing external rhythmic cueing, could be used in spontaneous speech, e.g. conversation, but with a possible cost to fluency due to more variable effect. Combining approaches, and carefully monitoring temporary fluency induction, could optimise outcomes.

3.6 Conclusions

In this study, I found that choral speech practice increased speech fluency in adults who stutter on sentence reading, but the size of this increase was not significantly modulated by A-TDCS to the left IFC. Fluency during two additional speaking tasks - passage reading and conversation – was not significantly increased following TFI with choral speech, either with or without A-TDCS. However, there was a trend towards stuttering reduction in passage reading and conversation, following TDCS coupled with induced fluency, which gives some indication of a positive modulation of fluency that could be stabilised and increased using a mutiple-session TDCS approach. Stuttering varied considerably among individuals and between sessions and may have obscured the expected positive effects of TDCS on fluency. Lasting fluency is notoriously difficult to achieve for adults with persistent development stuttering. Therefore, the appeal of TDCS to improve therapy outcomes is clear. Even though I found no significant effects of a single session of TDCS on speech fluency in people who stutter, I identified several factors that informed the multiple TDCS session approach, implemented in the randomised controlled trial described in chapter 4 of this thesis.

Chapter 4

A randomised controlled trial of A-TDCS as an adjunctive therapy for adults who stutter

4.1 Summary

Developmental stuttering reduces speech fluency, which can have far-reaching negative consequences for participation in social roles, and quality of life. As such, it represents a considerable burden to individuals living with this speech condition, and to society. The outcomes of behavioural therapies targeted to reduce disfluency are limited: trained fluency is effortful and comes at a cost to speech naturalness, and long-term fluency is rarely achieved. A-TDCS as an adjunct to behavioural therapy can improve outcomes in acquired disorders of the motor, and speech and language systems, which indicates a possible application to increase speech outcomes for adults who stutter.

This chapter describes a randomised controlled trial (RCT) testing whether A-TDCS applied over left IFC during TFI could result in lasting fluency in adults with developmental stuttering. Thirty adult men with moderate to severe developmental stuttering received either A-TDCS over left IFC (n=15) or sham stimulation (n=15) delivered during TFI behavioural intervention for 20 minutes daily over 5 days. The primary outcome of the trial was measured by change in speech disfluency, at 1 and 5 weeks following intervention. Secondary measures were the changes in standardized assessments of stuttering severity and psycho-social impact of stuttering. I also conducted exploratory analyses of the effects of A-TDCS during the intervention (immediately preceding and following TFI in each session) and across the speaking tasks. Finally, I explored the effect on different disfluency types (stutters and other disfluencies).

I found a significant effect of A-TDCS on the primary outcome measure. Disfluency was significantly reduced in the A-TDCS group compared with the sham group for at least 5 weeks following intervention. The effect at 5-week follow-up was driven by the reduction in disfluency during reading, rather than conversation. Stuttering severity, measured by SSI, reduced in the A-TDCS group relative to sham across 1- and 5-week time points. The negative psycho-social impact of stuttering reduced in both the A-TDCS and the sham group 5 weeks following intervention, but there was no significant difference between the groups.

The exploratory analysis of effects over the course of the 5 day intervention revealed significantly greater reductions in disfluency in the A-TDCS group, relative to the sham group (who showed no lasting effects of TFI). Exploratory analysis of the effects on different types of disfluency showed a significant effect of A-TDCS 1 and 5 weeks following intervention, relative to sham, which was evident for all types of disfluency, with no significant differences between types.

In conclusion, a 5 session intervention with A-TDCS to left IFC resulted in a reduction of the speech impairments that characterise developmental stuttering, which persisted for at least 5 weeks. A-TDCS reduced both core stuttering characteristics, and other speech disfluencies that can indicate avoidance behaviours, which serve to reinforce and maintain stuttering. The effects of A-TDCS were specific to the speech impairments of stuttering, although participation in the trial reduced negative psycho-social impact of stuttering for both the A-TDCS and sham group. These results indicate a clinical application for A-TDCS in interventions to increase fluency in adults who stutter.

4.2 Introduction

4.2.1 Limitations of speech therapy for adults who stutter

Developmental stuttering during adulthood represents a considerable burden to society. It has been associated with reduced educational and employment opportunities, social anxiety and compromised quality of life, as discussed in the general introduction to this thesis. Adults who stutter are highly unlikely to recover fully, but behavioural therapies can reduce overt stuttering behaviours. Direct work on speech fluency may involve fluency-shaping therapy, aimed at changing the motor patterns for articulation and voicing to reduce the likelihood of stuttering, or block modification therapy, aimed at reducing tension in moments of stuttering. Common to both approaches, fluency improvements do not persist without continued practice, and can be difficult to fully integrate into everyday speech. Furthermore, learning these new speech patterns can compromise speech naturalness, which can reduce the acceptability of these approaches to adults who stutter (Metz et al., 1990; Onslow et al., 1992; Runyan et al., 1990; Teshima et al., 2010). Therefore, methods to improve therapy outcomes for adults who stutter are valuable. Combining A-TDCS with speech therapy for adults who stutter could potentially produce faster, larger, more stable or longer lasting fluency improvements than behavioural therapy alone.

4.2.2 Methods for Temporary Fluency Induction (TFI)

There are numerous methods for temporarily inducing near complete fluency in adults who stutter, as described in the general introduction. These methods share characteristics, such as perturbing or enhancing sensory information regarding speech, or providing external cues to timing. In chapter 3, I investigated the use of

choral speech, as a means to induce immediate fluency, in combination with A-TDCS. Choral speech is a particularly effective TFI method. The effects of choral speech on stuttering have been studied since the early 20th century, and the method has a consistent, dramatic effect, reducing stuttering by up to 100 percent (Cherry et al., 1956; Kalinowski & Saltuklaroglu, 2003b; Andrews et al., 1983; Kiefte et al., 2008). However, as choral speech can only be used when reading, it has limited clinical utility and ecological validity.

Metronome-timed speech is also an effective TFI method (Davidow et al., 2009), and it can be combined with more functional, every day speech communication. Metronome-timed speech involves producing rhythmic speech with even distribution of stress, by timing each syllable to an external metronome beat. The effects of metronome-timed speech, like all TFI methods, do not persist when the technique is withdrawn (Ingham, 1982; Davidow et al., 2009). However, metronome-timed speech has been used as a basis for therapy in the past with limited success (Andrews, 1965), and has also been trialled more recently specifically for pre-school children (Coppola et al., 1982; Trajkovski et al., 2009; Trajkovski et al., 2011). In this context, matching to an external metronome stimulus is used minimally. Instead, the focus is on imitation of a rhythmic speech pattern modeled by a therapist or care-giver, i.e. an internal isometric rhythm must be generated and maintained.

Choral speech and metronome-timed speech bring about changes in neural activation within the speech network, in regions that have shown abnormality in people who stutter. Both techniques have 'normalised' activations in STG, left IFC, cerebellum and in basal ganglia nuclei in adults who stutter, although there is variation between

studies in the regions affected (Wu et al., 1995; Fox et al., 1996; Toyomura et al., 2011; Toyomura, Fujii & Kuriki, 2015).

4.2.3 A-TDCS as an adjunctive therapy for neurological disorders

TDCS can increase learning, and its effects build and stabilize when applied in consecutive daily sessions (Reis et al., 2009; Baker et al., 2010). There are increasing numbers of studies of TDCS as an adjunctive treatment for disorders of motor, language and cognitive functions. The majority of these focus on impairments related to stroke. Although the results are variable, numerous studies do show clear benefits (Kang et al., 2016; Elsner et al., 2015) However, differences in stimulation protocols, as well as in duration of the intervention programmes, make it somewhat difficult to assess which parameters are critical for a positive outcome.

A meta-analyses of TDCS-aided motor rehabilitation in stroke, including studies using anodal, cathodal and bi-hemispheric protocols, reported an overall benefit of TDCS across protocols and stages of recovery (Kang et al., 2016). Ipsilesional A-TDCS has increased the outcomes of physical therapy following stroke in several studies (e.g. Allman et al., 2016; Khedr et al., 2013; Mortensen, Figlewski & Andersen, 2016). For example, ipsilesional A-TDCS of M1 during a 9-day rehabilitation programme of arm function improved clinical scores measures up to 3 months later (Allman et al., 2016).

A recent Cochrane systematic review concluded that RCTs using TDCS in aphasia have yet to prove the effectiveness of the approach in improving everyday communication ability (Elsner et al., 2015). However, TDCS studies, using various protocols, have shown improved language rehabilitation in this clinical population

(see reviews by Holland et al., 2012; Monti et al., 2013; Sandars et al., 2016). For example, anomia (difficulty producing words, particularly nouns) was improved when tested 1 week following a 5-day intervention combined with A-TDCS over left IFC (Baker et al., 2010). Most relevant to the current trial, speech motor skill was improved in patients with acquired apraxia of speech following stroke, in two small studies using A-TDCS over left IFC. In the first, three patients received uni-hemispheric stimulation (cathode on right SOR) combined with daily speech therapy over 5 days, compared to sham (Marangolo et al., 2011), and benefits persisted at follow-up 2 months later. In the second, eight patients received bi-hemispheric stimulation (cathode on right IFC), combined with daily speech therapy over ten days, compared to sham (Marangolo et al., 2013), and benefits persisted at 1-week follow-up. The very small sample sizes preclude strong conclusions, but suggest that further studies of speech motor rehabilitation are warranted.

The use of A-TDCS in neurodevelopmental disorders of speech has not been investigated. This may be due to an understandable caution regarding using the method with paediatric populations. However, there is considerable room for improving the outcomes of therapy for adults living with persistent developmental difficulties. The feasibility study reported in Chapter 3, was the first to investigate the use of A-TDCS in therapy for developmental stuttering. Although I found no significant benefits from a single application of A-TDCS, mutiple-session A-TDCS studies have shown that unstable effects, observed following the initial intervention session can increase and stabilize following subsequent sessions (e.g. Reis et al., 2009; Baker et al., 2010).

4.2.4 Research questions

I completed an RCT that aimed to explore the use of A-TDCS over left IFC as an adjunctive therapy for development stuttering, delivered in 5 consecutive daily sessions. Left IFC was identified as the stimulation site as it has a critical role in speech production, and under-activity in this region is implicated in developmental stuttering. As for the single session feasibility study described in Chapter 3, I chose to use TFI in combination with A-TDCS, to gain immediate and maximal fluency during the intervention. In the single-session study, A-TDCS combined with choral speech did not result in significant reduction in disfluency, but I gained useful insights about how outcomes could be increased. The current study has been informed by these insights. I was interested in using both choral and metronome-timed speech to provide task variation and difficulty, which is recognized to improve therapy outcomes (e.g. Knock et al., 2000), and to increase ecological validity. Both methods were used only for temporary fluency induction, i.e. I did not train maintenance of an internalised metronome rhythm following metronome-timed speech.

I chose a range of outcomes measuring the core speech impairment of stuttering and its psycho-social impact. The primary outcome was a sensitive measure of change of speech impairment, based on frequency of symptoms (percentage of disfluent syllables produced: % ds). I included assessment of % ds in more controlled (reading) and more functionally relevant (conversation) contexts. Secondarily, I included two standardised clinical measures. The Stuttering Severity Instrument: SSI-4 (Riley, 2009) measures symptoms of stuttering including duration of stuttering moments and physical concomitants. The Overall Assessment of the Speaker's

Experience of Stuttering (OASES: Yaruss & Quesal, 2006) is a self-assessment of the impact of living with a stutter, including psycho-social factors.

To improve sensitivity to detect change in symptoms, I aimed to keep the experimental groups as homogeneous as possible by recruiting only male, right-handed, participants with at least a moderate stutter severity. In addition, I measured all speech disfluencies, rather than only 'core' symptoms. Finally, I did not include any repeated stimuli, in order to avoid unwanted adaptation effects.

4.2.5 Measuring trial outcomes

I measured the effect of A-TDCS on the primary and secondary outcomes of the intervention, at 1- and 5-week follow-up. I predicted that the TFI intervention when combined with A-TDCS, relative to sham, would result in a lasting reduction in the primary outcome: disfluency measured at 1 and 5 weeks post-intervention. I also predicted that, relative to sham, A-TDCS would decrease stuttering severity measured by SSI-4 at 1 and 5 weeks post-intervention, and would decrease the negative psycho-social impact of stuttering, measured by OASES, 5 weeks post-intervention. These were the secondary outcome measures. TFI combined with sham stimulation was predicted to have no lasting effect on any outcome.

4.2.6 Exploratory analyses

In addition to the trial outcomes, I conducted exploratory analyses to further understand the effects of A-TDCS. To investigate effects over the course of intervention, disfluency was assessed during reading aloud and conversation, immediately pre and post TFI on each of the 5 intervention sessions. I predicted that

the sham group would not show any significant change in disfluency measured pre and post TFI at each session. In contrast, I predicted that the A-TDCS group would show a reduction in disfluency post TFI at each session, resulting in a significant difference between the groups. I also predicted larger decreases in disfluency in the A-TDCS group as the intervention progressed (measured pre and post TFI), resulting in an increase in the difference relative to sham over the 5 intervention sessions.

Finally, I completed exploratory analyses of the effects of A-TDCS between the different speaking tasks, and different disfluency types. In the main analysis of outcomes, I chose to test the change in the percentage of disfluent syllables (% ds), as any increase in overall speech fluency would be a positive clinical outcome. However, a differential effect of A-TDCS between the two tasks (reading and conversation), or between types of disfluency (stutters, other disfluencies) could inform future work establishing the most effective combination of TDCS with behavioural intervention. I tested whether A-TDCS affected fluency in reading and conversation differently, and whether the effects measured at 1- and 5-week follow-up varied between stuttered and other types of disfluency.

4.3 Methods

4.3.1 Trial design

The study had a double-blind, sham-controlled, parallel-group design to test the effect of A-TDCS when combined with TFI intervention. The primary outcome measure was clinical assessment of speech fluency, assessed at two baseline time points and at two time points following intervention, using reading and conversation tasks. Secondary outcome measures were standardized clinical measures of stuttering severity (assessed once at baseline and at both time points following intervention) and a self-report of the psycho-social impact of stuttering (assessed once at baseline and at the final time point). Further measures included verbal fluency (phonemically cued), and self-reports of anxiety, and communication attitudes. These measures were included at baseline to test that the study arms were well matched on a range of factors relevant to a diagnosis of developmental stuttering. I also repeated all measures at the final outcome point, for completeness, and these results are included in appendix 4. A range of magnetic resonance imaging measures were taken before and 1 week following the intervention. These measures are not reported here but are mentioned for completeness. Figure 1 shows the study design and time-line. The NRES Committee South Central Oxford C: (11/SC/0482) approved the study. Participants gave informed written consent to participate in the study, in accordance with the procedure approved by the committee.

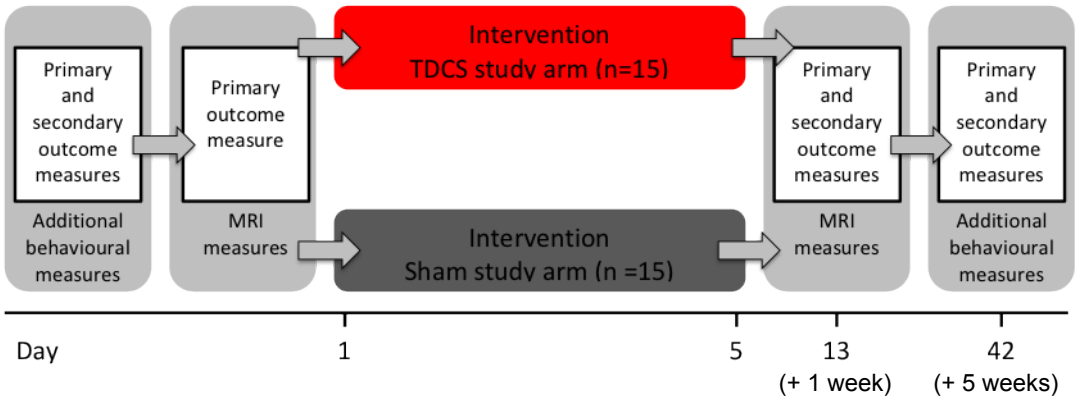


Figure 16: RCT design and time line

4.3.2 Participants

A community sample of 71 adult men who stutter were assessed for eligibility for the study. Inclusion criteria were male gender, age in the range 18-50 years, right-handedness, English as a native language and at least a moderate stuttering severity, assessed by SSI-4. Exclusion criteria included any disorder of speech, language or communication other than developmental stuttering, sensory impairment, neurological or psychiatric illness or any safety contra-indication for TDCS. Thirty of the 71 screened participants met these eligibility criteria and were randomly allocated to the A-TDCS or sham treatment study arms. As a registered Speech and Language Therapist, I confirmed the diagnosis of developmental stuttering in all participants during the first baseline assessment. Trial sessions were conducted in the Department of Experimental Psychology, University of Oxford, or in participants' homes or workplaces, according to participants' preference or availability. The study is registered with ClinicalTrials.gov (NCT02288598) and was conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines.

4.3.3 TFI behavioural intervention

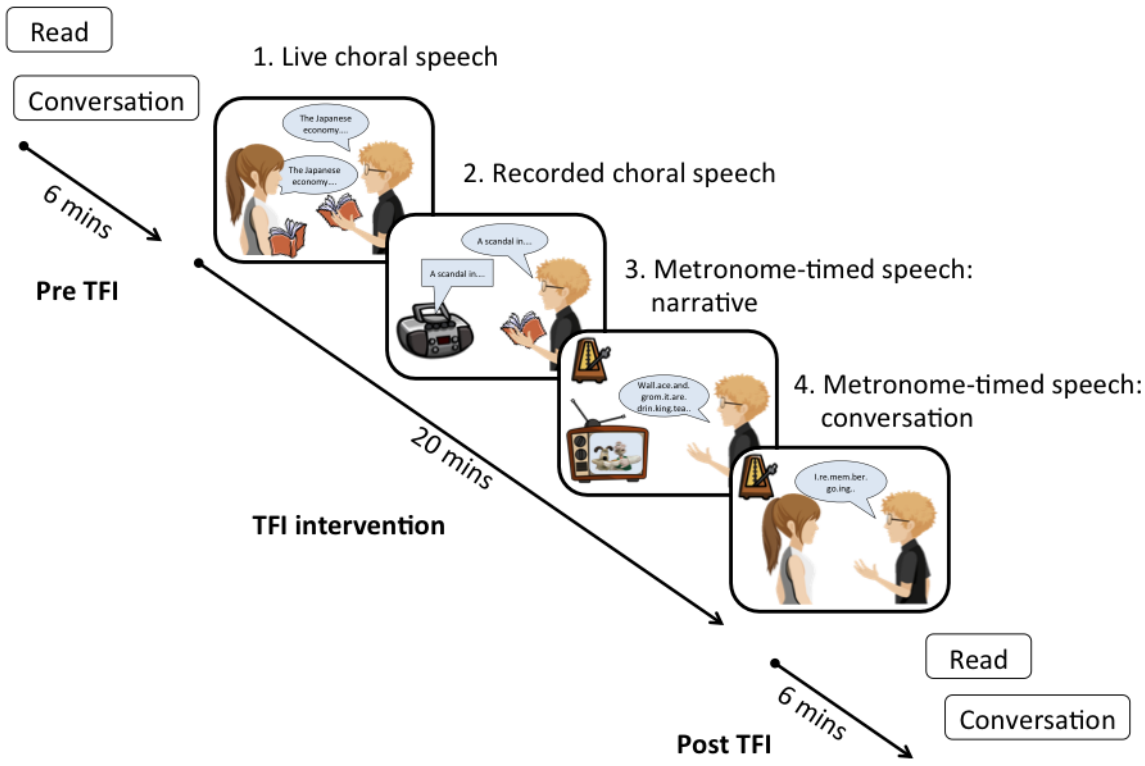
The intervention involved 20 minutes of TFI intervention over 5 consecutive days. As a registered Speech and Language Therapist, I delivered the intervention. Participants completed 4 tasks in a set order on each day of intervention. Tasks 1 and 2 used choral speech to induce fluency, and tasks 3 and 4 used metronome-timed speech (see figure 17 for illustration of a single intervention session). The task order was designed to form a hierarchy of difficulty, and the metronome rate in the metronome-timed speech tasks also increased over the 5 sessions. The intervention aimed to maximize fluency during every session, however the hierarchy of difficulty was included to maintain engagement in the tasks, and to increase functional relevance. I modeled tasks on day 1 of the intervention, and participants were given feedback as needed in all sessions, to support them to maintain adequate task performance to induce fluency. If any participant was unable to complete a task after it was modeled several times, the task was omitted from intervention and the remaining tasks were extended so that intervention was always delivered for 20 minutes per session. I measured task proficiency on a 5-point Likert scale for each task on each day.

Choral speech tasks 1 and 2:

Task 1 used choral speech with a live model voice. Participants read excerpts from a newspaper, in time with me. If necessary, I modified my speech rate to more closely match that of the participant, to maintain his fluency. Task 2 used choral speech with a recorded voice. Participants read passages from a novel, in unison with an audio recording. Participants were instructed to pause briefly if they were unable to keep pace with the recorded voice, at any time.

Metronome-timed speech Tasks 3 and 4:

For the metronome-timed speech tasks, metronome rate on day 1 was 140 bpm and progressed to 190 bpm by day 5. Participants were instructed to indicate if the rate exceeded a comfortable speaking rate. In this case, the metronome was slowed to a comfortable rate, and maintained at this rate for the remaining intervention sessions. Task 3 used metronome-timed speech with video stimuli. Participants narrated video clips of silent animations, synchronizing their speech to the metronome rate. In task 4, participants engaged in conversation with me using metronome-timed speech. The conversation topics were selected from a prepared list.



Pre and post TFI, participants completed reading and conversation tasks, for 3 minutes each. The order of these tasks was counter-balanced across participants. During the TFI intervention , participants completed four tasks in a set order - two using choral speech (1. live voice, 2. recorded voice) and two using metronome-timed speech (3. narrating a video, 4. conversation) - for a total duration of 20 minutes.

Figure 17: TFI procedure used in RCT

4.3.4 A-TDCS

In the A-TDCS study arm, participants received 20 minutes of stimulation at 1 mA, applied during the TFI intervention. The anode was placed over left IFC (centred on FC5 according to the 10-20 EEG electrode placement system), and the cathode over the right SOR. A Neuroconn direct current stimulator in 'study mode' was used to deliver TDCS (see section 4.3.11 on blinding procedure). The electrodes measured 5 cm x 7 cm, and were placed within saline soaked sponges; the anode was placed in portrait orientation (short side horizontal), and the cathode in landscape orientation (long side horizontal). The same electrode placement was used in the sham stimulation study arm, during which the current was ramped up over 15 seconds, maintained for 15 seconds at 1 mA and ramped down over 15 seconds at the start of the session. The parameters for sham stimulation delivered current at an ineffective dosage. However, the initial ramping of current produces an itching or tingling sensation as for TDCS stimulation.

4.3.5 Speech analysis

Speech samples were taken at two baselines sessions prior to the 5-day intervention, at the pre- and post TFI time points during each session of the intervention, and at 1- and 5- week follow-up. Speech samples always comprised one sample of reading and one sample of conversation. The reading task involved reading aloud a newspaper excerpt. This was self-paced and timed with a maximum duration of 3 minutes (participants occasionally completed the excerpt within 3 minutes). The conversation task involved engaging in conversation with me for 3 minutes, on a topic from a prepared list. All speech samples were video recorded, and the recordings were used for offline analysis of speech fluency.

A detailed speech analysis was completed for all speech samples, which allowed additional exploratory analysis of effects of A-TDCS on types of disfluency and across tasks, as well as the primary outcome measure of the overall effect on disfluency. For each sample, I took counts of the total number of syllables and the number of disfluent syllables. Disfluent syllables were categorized into stuttered syllables (ss) and other disfluent syllables (os). Stuttered syllables were defined as those in which a phoneme, or the entire syllable, was repeated or prolonged, or a tense pause (block) was produced. Other disfluent syllables were defined as those within a repeated multi-syllabic word or a phrase, syllables within a revised phrase, a word fragment or an interjection ("um", "err") (Guitar, 2014; Ward, 2006).

Inter-rater reliability was measured by comparing the stutter counts I completed with those from an additional researcher who analysed all speech samples from two participants, selected at random. A strong intra-class correlation was found for the inter-rater measurements (ICC = .94, $p < .001$), indicating a high level of reliability. Both the researchers completing the speech analyses were blind to stimulation condition, and the second researcher was also blind to the time point at which the speech samples were taken.

4.3.6 Primary outcome measure

The primary outcome measure for the trial was the percentage of disfluent syllables (% ds) in each sample. I calculated % ds by summing the disfluent syllables (ss and os) for each speech sample, and expressing this number as a percentage of the total syllables for the sample. Baseline fluency was taken as the average of the two

baselines Outcomes were measured as the change in % ds during reading and conversation at 1-week and 5-week follow-up, relative to baseline % ds.

4.3.7 Secondary outcome measures

Stuttering Severity Inventory, 4th edition (SSI-4: Riley, 2009)

SSI-4 is a norm-referenced assessment of stuttering severity. The frequency of stuttering, the average duration of the three longest stuttered syllables, and the type and severity of physical concomitant behaviours are each converted to scale scores, and summed to give an overall score. These measures were taken from a 3-minute sample of reading and a 3-minute sample of conversation.

Overall Assessment of the Speaker's experience of Stuttering (OASES: Yaruss and Quesal, 2006)

I used the OASES to measure the psycho-social impact of living with a stutter. The OASES is a 100-item standardized self-report questionnaire of the overall functional impact of living with a stutter. Impact is measured over 4 sections, relating to components of the World Health Organisation International Classification of Functioning, Disability and Health (2001): assessment of stuttering behaviour, reactions to stuttering, communication in daily situations, and quality of life. These are averaged to give an overall impact score. The OASES was administered at the first baseline visit, and at the 5-week endpoint only, as repeating the assessment at the 1-week time point would violate its internal validity.

4.3.8 Measures of effects during intervention

TFI Task effectiveness

The effectiveness of the TFI intervention was measured by assessing disfluency (% ds) during each of the TFI tasks. However, as it is possible to gain some fluency enhancement from an auditory masking effect alone during the TFI tasks, I also included a task proficiency rating to assess whether fluency enhancement was related to task engagement. I rated task proficiency on a 5-point Likert scale for each task on each day (1 = excellent, 2 = good, 3 = ok, 4 = poor, 5 = very poor).

Effects on speech fluency during intervention

I measured the percentage of disfluent syllables (% ds) during reading and conversation immediately before and after TFI intervention, on each day of the intervention. I used change in % ds, relative to baseline, to assess the effect of TDCS over the course of the intervention programme.

4.3.9 Measures of adverse effects

Speech naturalness

Speech naturalness is an important clinical outcome that can be negatively affected by behavioral interventions (Martin, Haroldson & Triden, 1984; Onslow et al., 1996; Teshima et al., 2010). I assessed speech naturalness for all speech samples using a nine-point Likert scale, with 1 representing highly natural sounding speech and nine representing highly unnatural sounding speech. Neither the behavioural intervention nor the TDCS treatment reduced speech naturalness, relative to baseline, measured at the post-intervention time points (details of this analysis is provided in appendix 3, table A3).

TDCS adverse effects questionnaire

TDCS has been associated with mild and transient adverse effects such as an itching or tingling sensation at the electrode sites. Adverse effects related to receiving TDCS were monitored in both groups, using a questionnaire recommended from a previous review of TDCS adverse effect reporting (Brunoni et al., 2011). Participants in both groups reported some adverse effects during intervention (commonly, itching or tingling under the electrodes). The mean ratings for each group fell between 'absent' and 'mild', and these sensations did not differ between groups (details of this analysis is provided in appendix 3, table A2.).

4.3.10 Additional measures

Beck anxiety inventory (BAI: Beck et al., 1988)

As there is an increased prevalence of anxiety in developmental stuttering, I monitored anxiety symptoms during the trial. The BAI is a 21 item self-report inventory to measure severity of anxiety. The maximum score is 63, which indicates severe anxiety. I administered the BAI at the first baseline visit and at the final time point following intervention.

Modified Erikson S24 scale of communication attitudes (Andrews & Cutler, 1974)

In addition to the OASES impact measure, I also included the S24, which measures person's attitude towards communication in a range of settings Communication attitudes are assessed using a self-administered questionnaire. Participants give a yes/no response to 24 statements regarding communication, e.g. "I find it easy to talk with almost anyone". The assessment is scored out of 24, according to the number of

responses given that are consistent with a negative attitude towards communication, i.e. higher scores indicated a more negative attitude. I administered the S24 at the first baseline visit and at the final time point following intervention.

Phonemic fluency

I included a phonemic fluency task, which involves production of words beginning with a given phoneme within a 1-minute time limit. The task was repeated for three phonemes (/p/, /f/, /l/). Performance on this type of fluency task depends on a range of cognitive and language factors, e.g. vocabulary, size, lexical access, executive control. It is best described as a test of general verbal functioning, although performance is also limited by speech motor skills.

Magnetic resonance imaging measures

A range of MR measures were taken. These included T1 weighted structural imaging, speech task fMRI, resting-state fMRI, magnetic resonance spectroscopy and DTI.

The additional behavioural measures were taken at initial screening visit and repeated at 5-week follow-up, and these results are reported in appendix 4. The MRI measures were taken at the second baseline, and repeated at 1-week follow-up. They are not reported here, but are mentioned for completeness, the rationale for including them is discussed in chapter 5.

4.3.11 Randomisation and blinding

A researcher who was not involved in any aspect of the trial performed the randomisation of participants into the sham and TDCS study arms. The allocation list

was password-protected and only accessible for unblinding following completion of data processing. Participants were assigned to study arms on day 1 of intervention, using blocked randomization. A block size of four was chosen generating six random sequences: AABB, ABAB, ABBA, BAAB, BABA, and BBAA. One of the sequences was chosen randomly until all six had been chosen, one sequence was repeated and the last pair were allocated randomly to A and B so that all 30 participants were assigned to one or other study arm (according to the procedure described by Roberts & Torgerson, 1998). Allocation concealment was achieved by assigning a unique 5-digit code per participant, used to set the stimulation parameters for TDCS or sham stimulation using the DC stimulator study mode. Codes remained in sealed sequentially numbered envelopes until allocation. The stimulator study mode displays no identifying information to the operating researcher, and so enabled me to remain blind to stimulation condition after allocation and throughout the study. I enrolled all participants into the study, and also completed all clinical assessments, operated the DC stimulator and administered all intervention sessions. All participants were also blind to stimulation arm. Due to a technical problem with the stimulator, two participants received stimulation on days 4 and 5 using a DC stimulator without study mode. An additional researcher was used to operate the new stimulator in these sessions, so that I remained blind to stimulation arm.

4.3.12 Statistical analysis

The speech data significantly deviated from a normal distribution (reading % ds: Shapiro-Wilk = .82, $p < .001$; conversation % ds: Shapiro-Wilk = .73, $p < .001$; SSI-4: Shapiro-Wilk = .82, $p < .001$). One possibility was to transform the data (as done in chapter 3), and then perform ANCOVAs on transformed data. However, reporting

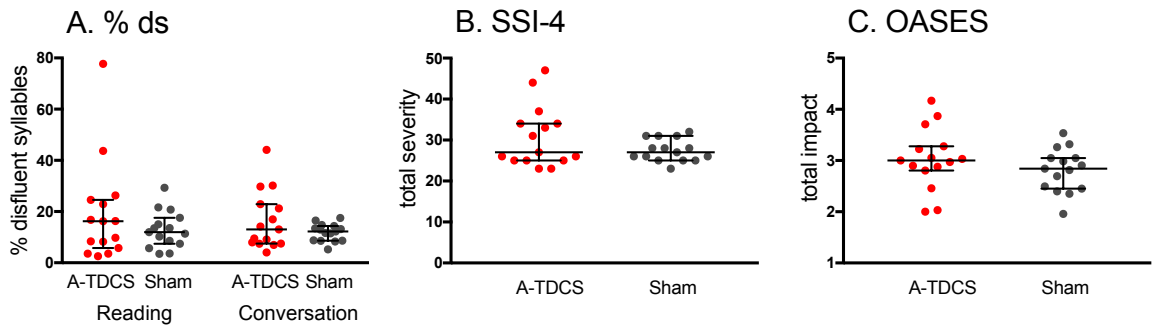
confidence intervals for the data in interpretable units becomes problematic (Bland & Altman, 1996). The primary and secondary outcomes for the trial were defined in terms of change from baseline values. As the change scores (i.e. baseline subtracted) were approximately normally distributed, I used these scores in ANOVAs, for all analyses of the effects of A-TDCS. Use of change scores also controlled for individual differences in the baseline scores. Change scores can be vulnerable to regression to the mean (Vickers & Altman, 2001;Barnett, van der Pols & Dobson, 2005). Our design reduced this possibility by using a randomly allocated control group and multiple baselines (Barnett et al., 2005).

4.4 Results

4.4.1 Clinical characteristics

All 30 participants completed the intervention and none were lost to follow-up (see Consort flow diagram, appendix 2, figure A4). Recruitment commenced in October 2014 and was completed in February 2016. Follow-up commenced in December 2014 and was completed in March 2016.

Baseline performance for all participants on the three outcomes measures is shown in Figure 18 (A: % disfluent syllables, B: SSI-4, C: OASES total impact score; group medians are also reported in table 4 in the trial outcomes section along with the group data at follow-up). Mann-Whitney U tests confirmed that the groups did not significantly differ at baseline, on any outcome measure. In addition, the groups did not significantly differ on any other clinical or demographic characteristics at baseline (see table 4).



A shows percentage of disfluent syllables during reading and conversation. B shows SSI-4 total severity (maximum score is 46). C shows OASES total impact score (maximum score is 5). Individual scores are plotted for the A-TDCS (red) and sham (grey) groups with group median line and error bars showing the inter-quartile range.

Figure 18: Baseline scores for primary and secondary outcome measures

One participant in the A-TDCS group was an extreme statistical outlier with regard to baseline stuttering, i.e. he had values for both % ds and SSI-4 that were over three times the interquartile range of the sample. However, this participant did not have outlying change scores, except in % ds at 5 weeks after intervention (where he showed the greatest reduction in disfluency in the sample). Data from all participants were included in the primary analysis, according to the intention-to-treat principle. However, I also completed sensitivity analyses (Thabane et al., 2013) by re-running all analyses excluding this participant, to evaluate the robustness of the treatment effect.

Intervention was modified for one participant, who was able to produce only very minimal speech during the metronome-timed speech conversation task, due to the task demands (this was not the same participant whose data were extremely outlying at baseline). For this participant, metronome-timed speech in conversation was replaced with an additional choral speech live task. Level of disfluency during the TFI tasks was very low for both groups, and task proficiency scores were high, indicating that the TFI tasks were effective, and all participants engaged to a good level in the intervention. Details of those analyses are provided in appendix 3.

Table 4: Baseline demographic and clinical characteristics.

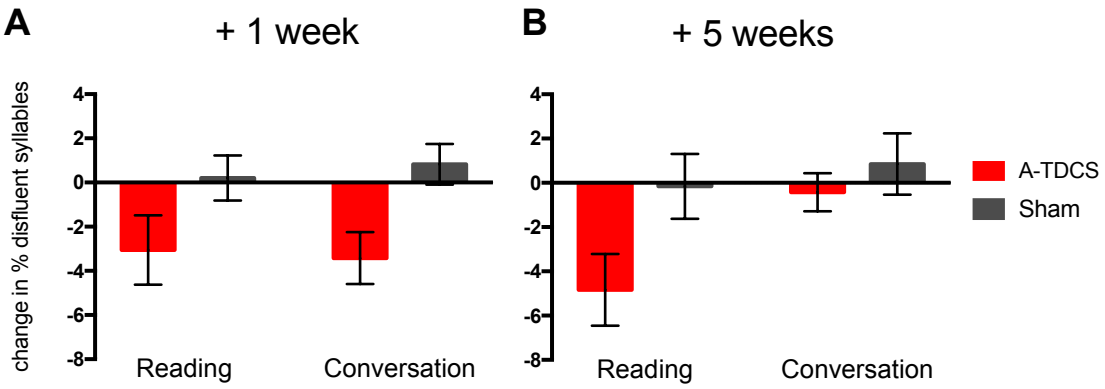
	A-TDCS (n=15) **mean (s.e.m.)**	**Sham (n=15)** **mean (s.e.m.)**
Age at intervention (years)	34.22 (2.08)	33.25 (2.26)
S24 (max. 24)[1]	17.47 (1.41)	15.93 (1.08)
Phonemic fluency[2]	36.47 (3.73)	40.27 (3.59)
	median (IQR)	**median (IQR)**
BAI (max. 63)[3]	11.00 (22.00)	7.00 (12.00)
Speech naturalness (1 – 9)[4]	5.50 (2.75)	5.00 (3.00)

[1]S24 scores range from 0 to 24, with 24 corresponding to the most negative attitude to communication. [2]Total number of words generated in 3 minutes, 1 minute each for letters *P, L, F*. [3]BAI scores range from 0 to 63, with higher scores indicating more severe anxiety. [4]Speech naturalness ratings ranged from 1 to 9, with 1 being highly natural sounding speech.

4.4.2 Trial outcomes

Primary outcome

The primary outcome for the trial was reduction in disfluency, measured 1 and 5 weeks after the end of intervention. To test how combining A-TDCS with TFI affected this outcome, I ran a mixed model ANOVA on % ds change scores, with stimulation group (A-TDCS, sham) as the between subjects factor and speaking task (reading, conversation) and time point (+ 1 week, + 5 weeks) as within subjects factors. Figure 19 shows disfluency reduction for the A-TDCS and sham groups, during reading and conversation, at each time point after the intervention.



Mean change in disfluency for the A-TDCS (red) and sham (grey) groups, one (A) and five (B) weeks after intervention. Mean change in percentage of disfluent syllables (baseline subtracted) is shown during the reading and conversation tasks at each follow-up. Error bars show s.e.m.

Figure 19: Post-intervention change in disfluency

Across tasks and time points, disfluency was significantly reduced for the A-TDCS group relative to the sham group (main effect of stimulation group, $F_{1,28} = 7.21$, $p = .012$, fig. 19). The effects of A-TDCS on disfluency during each speaking task varied differently over time (interaction between stimulation group, task and time $F_{1,28} = 4.77$, $p = .037$, fig. 19). The three-way interaction was examined using repeated-

measures ANOVA for each group separately with factors of task and time point. For the A-TDCS group, there was a significant interaction between task and time point ($F(1,14) = 11{\cdot}13$, $p = {\cdot}005$; figure 19 red bars) and this was not significant for the sham group ($F < 1$, $p = {\cdot}786$; figure 19, grey bars). Examination of the means for the A-TDCS group (figure 19, red bars) suggests that the task by time point interaction was due to maintenance of the reduced disfluency relative to baseline for the reading task at 5 weeks (no significant difference between time points) but a return to baseline disfluency levels for the conversation task (main effect of time point, $p = {\cdot}034$). Sensitivity analyses, excluding the participant with extremely high baseline disfluency, revealed an identical pattern of results.

In summary, disfluency 1 and 5 weeks after intervention – the primary outcome measure of the RCT – was significantly reduced in the A-TDCS group relative to the sham group. Although this effect was seen at both follow-up time points, and for both tasks, the effect at 5 weeks was driven by improvements during reading.

Table 5: Summary of change from baseline in the primary and secondary outcomes

	TDCS(n=15)		Sham(n=15)	
	1 week	5 weeks	1 week	5 weeks
	mean (s.e.m.)	mean (s.e.m.)	mean (s.e.m.)	mean (s.e.m.)
% ds read	**-3.05 (1.57)**	**-4.83 (1.62)**	0.21 (1.01)	-0.16 (1.46)
% ds conv	**-3.42 (1.17)**	-0.42 (0.85)	0.82 (0.92)	0.85 (1.38)
SSI-4	**-7.13 (1.36)**	**-3.40 (0.98)**	**-2.27 (1.03)**	-1.53 (0.93)
OASES	n/a	**-0.23 (0.10)**	n/a	**-0.13 (0.07)**

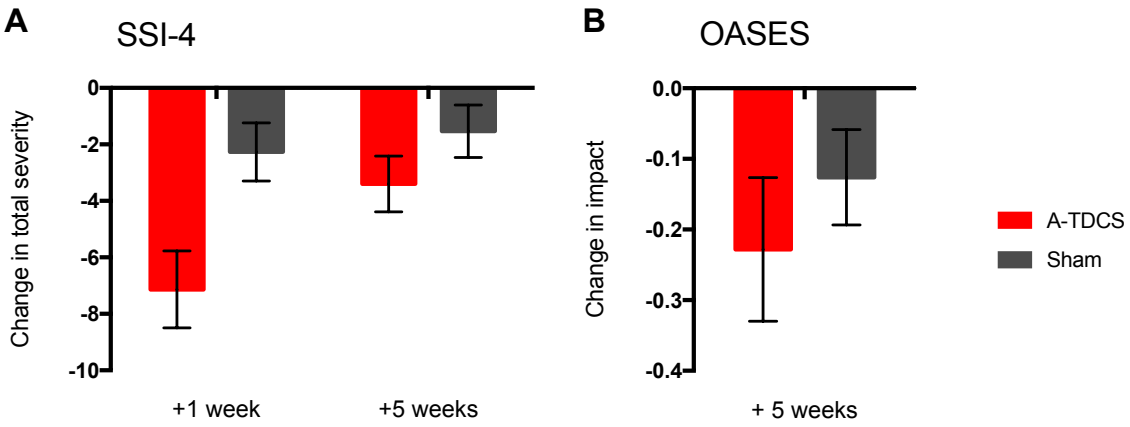
Table cells show mean change from baseline, with s.e.m. in parentheses. Significant differences from baseline are highlighted in bold ($p < .05$, one-tailed). n/a – not assessed

Secondary outcomes

Stuttering severity: SSI-4

I entered mean change in SSI-4 into a mixed model ANOVA with stimulation group (A-TDCS, sham) as the between subjects factor and time point (+ 1 week, + 5 weeks) as the within subjects factor. Figure 20A shows the change in stuttering severity following intervention, in the A-TDCS and sham groups. There was a significantly larger reduction in stuttering severity for the A-TDCS group than the sham group across both time points, (main effect of stimulation group, $F_{1,28} = 6.31$, $p = .018$; fig. 20A). The reduction in stuttering severity was significantly larger at 1-week post-intervention than at 5 weeks, for both groups (main effect of time point: $F_{1,28} = 8.73$, $p = .006$; fig. 20A). The interaction between these factors was close to significance ($F_{1,28} = 3.94$, $p = .057$; fig. 20A). One-sample t-tests against no change from baseline, indicated that the decreases were significant for both groups at 1 week post-intervention but only the A-TDCS group at 5 weeks (see table 5). Sensitivity analyses on change in SSI-4, excluding the participant with extremely high baseline disfluency, revealed an identical pattern of results.

In sum, stuttering severity measured by SSI was significantly reduced in the A-TDCS group relative to the sham group. This was consistent with our primary outcome measure of disfluency, i.e. both measures of speech impairment showed reduced impairment following A-TDCS.



Mean change in SSI-4 (A) and OASES (B) for the A-TDCS (red) and sham (grey) groups. Error bars are s.e.m. NB) OASES was administered at baseline and five-week follow-up only.

Figure 20: Post-intervention change in secondary outcomes

Psycho-social impact of stuttering: OASES

I used independent samples and one sample t-tests to test the change in the psycho-social impact of stuttering within and between the groups 5 weeks following the intervention. Figure 20B shows the change in total OASES score following intervention, in the A-TDCS and sham groups. Both the A-TDCS and the sham group showed significant reductions in the negative psycho-social impact of stuttering, relative to baseline level (A-TDCS: $t_{14} = -2.23$, $p = .021$; sham: $t_{14} = -1.86$, $p = .042$; one-tailed, fig. 20B). However, there was no significant difference between the groups in the size of the reduction (independent samples t-test, $t_{28} = -0.84$, ns). This indicates that, although A-TDCS in combination with TFI decreased the negative impact of stuttering, it did not do so more than the TFI intervention alone. Sensitivity

analyses, excluding the participant with extremely high baseline disfluency, revealed an identical pattern of results.

Summary of outcomes

Table 6 summarises the absolute mean difference between the groups (with the 95% confidence interval), indicating the treatment effects for each outcome. Effect sizes are also reported using Cohen's d. Clinical scores on the outcome measures at baseline, and at both follow-up time points are provided in table 7 for completeness.

I found that A-TDCS combined with TFI significantly reduced speech disfluency for at least 5 weeks following intervention. However, A-TDCS did not affect the negative psycho-social impact of the disorder more than behavioural intervention alone. Appendix 4 summarises the outcomes of the additional measures taken at 5-week follow-up, which are consistent with these main trial outcomes.

Table 6: Summary of the treatment effects - mean difference in change between A-TDCS and Sham groups, for primary and secondary outcomes

	Mean group difference		**Effect size (Cohen's d)**	
	1 week (95% CI)	**5 weeks (95% CI)**	**1 week**	**5 weeks**
% ds read	**-3.26 (-7.09 to 0.57)**	**-4.68 (-9.15 to -0.20)**	0.61	0.73
% ds conv	**-4.25 (-7.30 to -1.19)**	-1.27 (-4.60 to 2.06)	0.93	0.29
SSI-4	**-4.87 (-8.36 to -1.37)**	**-1.87 (-4.63 to 0.90)**	0.93	0.50
OASES	n/a	-0.10 (-0.35 to 0.15)	n/a	0.35

Table cells show mean difference in change between the A-TDCS and sham groups, for the primary and secondary outcomes, with 95% confidence intervals in parentheses. Significant group differences are highlighted in bold ($p < .05$, one-tailed). Effects sizes for the group difference are also reported using Cohen's d.

Table 7: Clinical outcome measures at baseline and follow-up, for the A-TDCS and sham groups

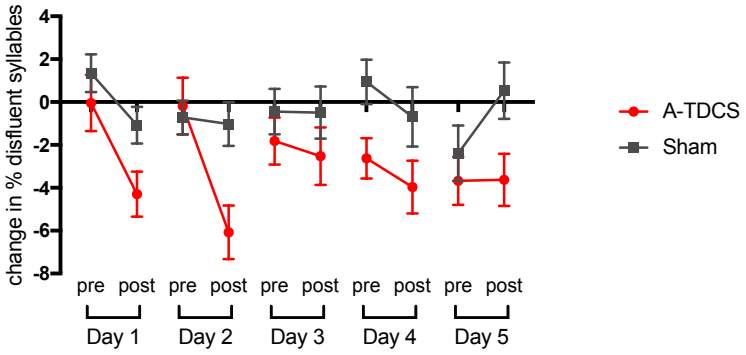
% ds reading	A-TDCS median (IQR)	Sham median (IQR)
Baseline	16.24 (18.83)	11.98 (10.18)
+ 1 week	8.77 (21.42)	12.60 (7.68)
+ 5 weeks	6.99 (15.78)	10.81 (8.56)
% ds conversation	**A-TDCS median (IQR)**	**Sham median (IQR)**
Baseline	13.03 (15.39)	12.26 (5.71)
+ 1 week	9.82 (9.38)	13.16 (4.90)
+ 5 weeks	13.42(14.36)	11.45(7.51)
SSI-4	**A-TDCS median (IQR)**	**Sham median (IQR)**
Baseline	27.00 (9.00)	27.00 (6.00)
+ 1 week	22.00 (13.00)	25.00 (6.00)
+ 5 weeks	26.00 (10.00)	27.00(4.00)
OASES total impact	**A-TDCS mean (SD)**	**Sham mean (SD)**
Baseline	3.03 (0.60)	2.81 (0.42)
+ 5 weeks	2.80 (0.73)	2.68 (0.51)

Table cells for % ds and SSI-4 show group median clinical scores at each time point. Inter-quartile ranges are in parentheses. SSI-4 has a maximum score of 46, indicating a very severe stutter. Group means are shown for the OASES, and standard deviations are in parentheses. Maximum score on OASES is 5, indicating a severe negative impact of stuttering.

4.4.3 Exploratory analyses

Effects of A-TDCS during intervention: Reading

Figure 21 shows the change in disfluency, relative to baseline, during reading over the course of the intervention. To test whether A-TDCS reduced disfluency after daily TFI, and if this reduction increased in magnitude over the 5 days, I calculated the within-session change (post TFI - pre TFI), and entered these change scores into a mixed model ANOVA with the between subject factor of stimulation group (A-TDCS, sham) and the within-subjects factors of day (1 to 5). These change scores are represented by the lines in figure 21, and also shown in figure 22A. The A-TDCS group showed significantly larger reduction in disfluency than the sham group, over the course of the intervention (main effect of stimulation condition, $F_{1,28} = 5.50$, $p = .026$). There was also a main effect of day, with a significant linear trend (main effect, $F_{4,112} = 7.00$, $p < .001$; planned linear contrast $F_{1,28} = 16.77$, $p < .001$), indicating that the magnitude of the disfluency reduction within each TFI session reduced as the intervention progressed. A-TDCS did not significantly modulate this effect.

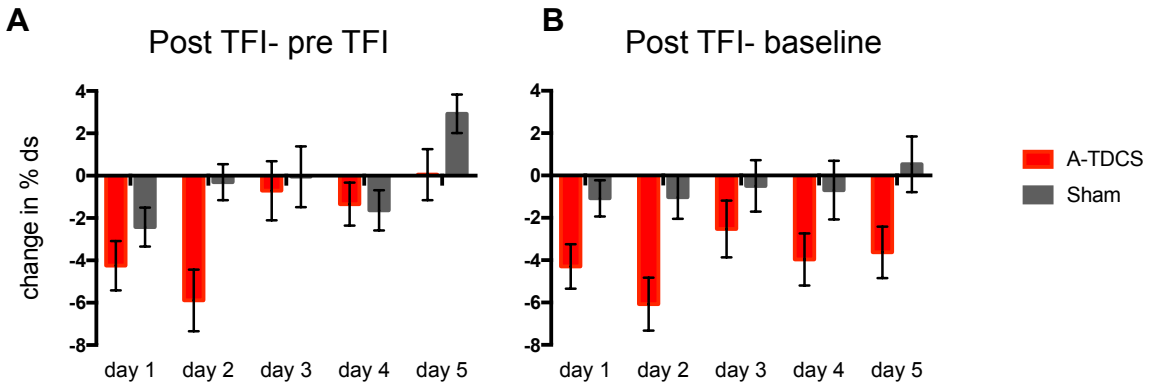


Mean change in disfluency (baseline subtracted) over the five day intervention, For the A-TDCS (red) and sham (grey) groups, immediately pre-TFI and post-TFI on each day. Error bars show s.e.m.

Figure 21: Change in disfluency during reading over the course of intervention

I also calculated the total change post TFI on each day, relative to the pre-intervention baseline, over the course of the intervention (i.e. the cumulative change

in disfluency; see post time points in fig. 21, and figure 22B). I entered these change scores into a mixed model ANOVA with factors of day and stimulation group and found a significant main effect of stimulation group, with greater fluency reductions following A-TDCS compared with sham ($F_{1,28} = 7.53$, $p = .010$). There was no main effect of day, or interaction with day, indicating that the effect of A-TDCS was stable across the course of the intervention. I also specifically tested change in fluency at the end of the training (post TFI on day 5) within each group, and between the groups. The sham group showed no significant difference in fluency from baseline (mean change = 0.53 (1.31), $t_{14} = 0.40$, ns). However, the A-TDCS group showed a significant reduction in disfluency (mean change = -3.63 (1.22), $t_{14} = -2.98$, $p = .005$, one-tailed), which was a significant difference from sham ($t_{28} = -2.32$, $p = .014$, one-tailed).



A shows mean within-session change in disfluency (post TFI - pre TFI) on each day of intervention. B shows mean change post TFI (baseline subtracted) on each day of intervention. Red bars are the A-TDCS group, and grey bars are the sham group. Error bars show s.e.m.

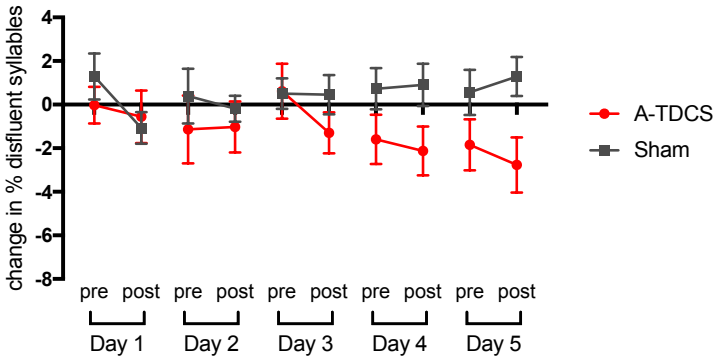
Figure 22: Within-day and cumulative change in disfluency during reading

A mixed model ANOVA which included both the within session change (post TFI – pre TFI on each day; figure 22A) and the total change scores (post TFI – baseline; figure 22B) as levels of the within-subjects factor 'change interval', revealed a significant

main effect of stimulation condition ($F_{1,28} = 8.40$, $p = .007$), but no significant interaction between stimulation condition and change interval. In sum, these results indicate that A-TDCS reduced disfluency during reading over the course of intervention. The stable effect on the total reduction in disfluency post TFI on each day indicates that the decreasing magnitude of the within-session reductions was balanced by increased retention of fluency between sessions, in the A-TDCS group.

Effects of A-TDCS during intervention: Conversation

Figure 23 shows the change in disfluency during conversation over the course of the intervention. As for the reading data, I first calculated change in disfluency within each session (post TFI – pre TFI; see lines in figure 23 and bars in figure 24A), and ran a mixed model ANOVA on these scores with the factors of day and stimulation group. I found no significant main effects or interactions between the factors.

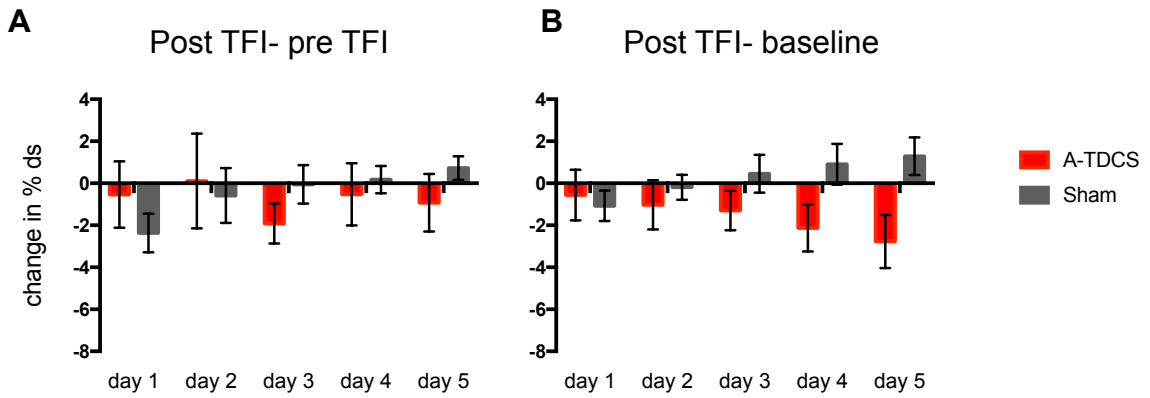


Mean change in disfluency (baseline subtracted) over the five day intervention, For the A-TDCS (red) and sham (grey) groups, immediately pre-TFI and post-TFI on each day. Error bars show s.e.m.

Figure 23: Change in disfluency during conversation over the course of intervention

I then tested the effect of A-TDCS on total reduction in disfluency at the end of each session, using the post TFI change scores (baseline subtracted; see post time points in fig. 23 and bars in figure 24B). There was no significant main effect of stimulation

condition, but the interaction between stimulation condition and day was close to significance, with a linear trend indicating that the A-TDCS group showed greater fluency reductions, relative to sham, as the intervention progressed ($F_{4,112} = 2.36$, $p = .057$; planned linear contrast $F_{1,28} = 4.19$, $p = .050$). T-tests on change in disfluency at the end of the training (post TFI on day 5), revealed no significant change in the sham group (mean change = 1.29 (0.89), $t_{14} = 1.44$, ns). However, the A-TDCS group showed a significant reduction in disfluency (mean change = -2.77 (1.26), $t_{14} = -2.19$, $p = .023$, one-tailed), which was a significant difference from sham ($t_{28} = -2.62$, $p = .007$, one-tailed).



A shows mean within-session change in disfluency (post TFI - pre TFI) on each day of intervention. B shows mean change post TFI (baseline subtracted) on each day of intervention. Red bars are the A-TDCS group, and grey bars are the sham group. Error bars show s.e.m.

Figure 24: Within-day and cumulative change in disfluency during conversation

Are the effects of A-TDCS on reading and conversation during the intervention different?

I was interested in whether the effects of A-TDCS were different across the two speaking tasks over the course of intervention. The separate analyses for the speaking tasks suggested that A-TDCS had a stronger effect during reading than conversation. I directly tested this by entering data from each task into a mixed

model ANOVA as levels of the within subjects factor 'task', in addition to the within-subjects factors of day and change interval (post TFI - pre TFI, post TFI - baseline), and the between-subjects factor of stimulation group. I found a significant main effect of task ($F_{1,28} = 5.70$, $p = .024$), but there was no significant interaction with stimulation group.

I also specifically assessed the effects of A-TDCS on the different speaking tasks at the end of the intervention, using the change score, relative to baseline on day 5 post TFI. A mixed model ANOVA with the between subjects factor of stimulation group, and the within-subjects factor of task showed that A-TDCS significantly reduced disfluency, relative to sham (main effect of stimulation group $F_{1,28} = 13.63$, $p = .001$), with no significant difference in effect between the tasks (no significant main effect of task, or interaction between task and stimulation group).

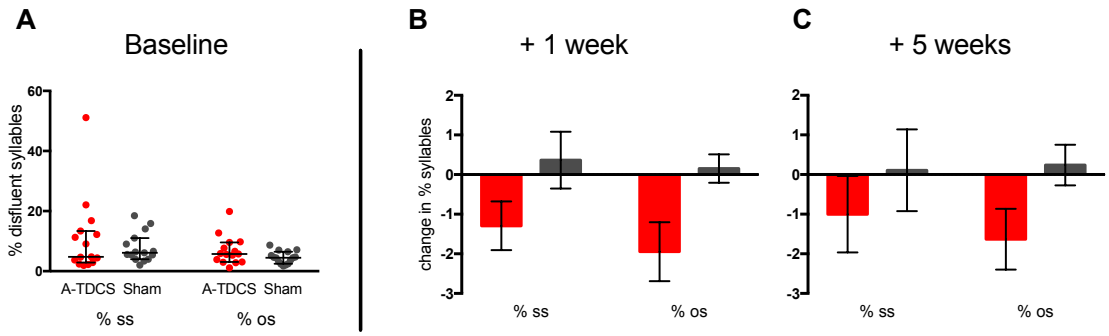
To summarise, A-TDCS significantly reduced disfluencies over the course of intervention during reading, relative to sham, and showed a trend in this direction during conversation. Although the changes following TFI were larger during reading for both the A-TDCS and sham groups, this difference between tasks was not modulated by A-TDCS. Critically, by the end of intervention, A-TDCS significantly reduced disfluency on both tasks, with no difference in effect between them.

Does A-TDCS have differing effects on stutters compared to other disfluencies?

Finally, I tested whether A-TDCS combined with TFI had different effects on stutters compared to other disfluency types, measured at 1- and 5-week follow-up (the main analyses tested change in all disfluencies). I tested change scores from baseline in a

mixed model ANOVA, with the between-subject factor of stimulation group (A-TDCS, sham) and the within-subjects factors of time point (+ 1 week, + 5 weeks), and disfluency type (stutter, other). Figure 25A shows baseline percentage of stuttered and other disfluent syllables, for reference, and figures 25B and C show the change in stuttered, and of other disfluent syllables following intervention.

I found a main effect of stimulation group ($F_{1,28} = 7.21$, $p = .012$), indicating that both disfluency types were reduced following A-TDCS relative to sham, across time points. There were no other significant main effects or interactions. So, A-TDCS reduced disfluencies of all types, with no significant difference in reduction between them.



A shows baseline percentage of stuttered syllables (% ss) and other disfluent syllables (% os), for the A-TDCS (red) and sham (grey) groups. Individual scores are plotted, with a line at group median and error bars showing the inter-quartile range.
B and C show group mean change (baseline subtracted) in both dusfluency types following intervention. B shows change at one-week follow-up and B shows change at five-week follow-up. Error bars show s.e.m.

Figure 25: Effect of A-TDCS on stuttered and other disfluent syllables

4.5 Discussion

This chapter described an RCT investigating the effect of combining A-TDCS over left IFC with TFI for 5 consecutive daily sessions, on measures of stuttering and its psycho-social impact up to 5 weeks following the intervention. I found a significant effect of A-TDCS, relative to sham, on the primary outcome measure of the trial, change in disfluent syllables during two speaking tasks. This effect persisted for at least 5 weeks, with effects at 5-week follow-up driven by increased fluency during reading. Consistent with this outcome, I also found a significant reduction on a standardised measure of stuttering severity when TFI was combined A-TDCS relative to sham, again persisting for at least 5 weeks. The final outcome measure, an index of the negative psycho-social impact of stuttering, was not significantly affected by A-TDCS. Both the A-TDCS and the sham group showed lower negative impact 5 weeks following intervention, with no significant difference between the groups.

In addition to measuring the outcomes of the trial, I also conducted some exploratory analyses to elucidate the effects of A-TDCS over the course of the intervention, and to test for any difference in effects between speaking tasks and types of disfluency. During the intervention, disfluency reduced significantly more in A-TDCS group, relative to sham. The effect was more robust during reading than conversation, but by the end of intervention, A-TDCS significantly reduced disfluency during both speaking tasks, with no significant difference between them. When I measured the effect of A-TDCS on different disfluencies at follow-up, I found that both stutters and other disfluencies were reduced, with no significant difference in magnitude of this reduction between types. I discuss these findings, and the implications of them, in the following sections.

4.5.1 Trial outcomes

Intervention combining A-TDCS with TFI significantly reduced disfluency at 1- and 5-week follow-up.

The primary outcome was change in disfluency at two time points following the intervention, which was measured during reading and conversation. I found that % ds reduced during both speaking tasks in the A-TDCS group, relative to the sham group, at 1-week follow-up resulting in a difference between the groups of 3 to 4 percentage points. At 5-week follow-up, the effects of A-TDCS were more variable. Disfluency during conversation was at baseline level for both the A-TDCS and the sham group. However, during reading, disfluency remained reduced in the A-TDCS group compared with the sham group (a difference of close to 5 percentage points between the groups).

The magnitude and the persistence of reductions in disfluency measured as the primary outcome indicate a clear clinical potential for A-TDCS as an adjunctive therapy. The changes expressed in terms of percentage of disfluencies within the speech samples appear modest. However, this is equivalent to a symptom reduction of 46 % in reading at 1-week follow-up and of 57 % at 5-week follow-up, relative to median baseline stuttering, for the group receiving A-TDCS (median % ds at baseline: 16.24, 1-week follow-up: 8.77, 5-week follow-up: 6.99), and a reduction of 25 % in conversation at 1-week follow-up for that group (median % ds at baseline: 13.03, 1-week follow-up: 9.82). Persistence of these changes for at least 5 weeks after intervention, during reading, is an important indicator of the clinical relevance of this approach. Assessment of benefits beyond the 5-week follow-up was not within the

scope of this study. However, the numerically (but not significantly) larger reduction of disfluency during reading at 5-week, compared to 1-week, follow-up suggests that the benefit may have persisted beyond the final time point of the trial. The measure of disfluency during conversation has more functional relevance than reading, but is more amenable to strategies to minimize overt disfluencies (and so, a less sensitive measure). Disfluency reduction was not as long lasting during conversation as for reading, and possible reasons for this task difference are discussed later.

Intervention combining A-TDCS with TFI significantly reduced SSI-4 score at 1 and 5-week follow-up.

The SSI-4 was included in the trial as a widely recognized standardized clinical measure, which provided complementary information to the primary outcome measure regarding fluency disruptions. In other words, % ds is a highly sensitive measure of stuttering frequency, whereas the SSI-4 sacrifices some sensitivity (by conversion to scaled scores), but incorporates important information regarding duration of stuttered moments, and of concomitant features such as twitch-like facial or body movements. The effects of A-TDCS measured by SSI-4 were consistent with those reported for the primary outcome: stuttering symptoms were significantly reduced relative to sham across both follow-up time points.

Interestingly, there was a significant reduction in stuttering from baseline in the sham group at 1-week follow-up only, although this was much smaller than for the A-TDCS group. We did not expect the TFI intervention alone to have any clinical benefit, and no such benefit was seen on our primary outcome. This suggests that the severity reduction in the sham group may have been in duration of stuttered moments, or

physical concomitant features, rather than frequency of stuttering, as these were the factors unique to the SSI-4. One possibility is that familiarity and practice with the tasks supported some alleviation of these symptoms, and that the 4-week interval between the 1- and 5-week follow-up sessions was sufficiently long for this effect to dissipate. However, this is entirely speculative.

Intervention combining A-TDCS with TFI did not significantly reduced the negative psycho-social impact of stuttering at 5-week follow-up, more than TFI alone.

No significant benefit of A-TDCS was found for the OASES self-assessment. However, both the A-TDCS and the sham groups showed decreased negative psycho-social impact following intervention. The OASES includes four sections assessing: 1) self-perception of impairment and understanding of stuttering treatment options, 2) reactions to stuttering, 3) communication in daily situations and 4) quality of life. Although we included the OASES as a measure of psycho-social impact, the assessment clearly has a broader scope, encompassing all domains of health and disability within the World Health Organisation framework (2001). The small changes on OASES total score seen in both groups may have been associated with involvement in the trial increasing understanding of the neurological basis of stuttering, and of potential future therapy directions (which is assessed in the first section of the assessment). Alternatively, psycho-social aspects of stuttering may have been directly affected through involvement in the research study (e.g. increased social contact during the study, experiencing a positive listener response to speaking under challenging conditions, making a valued contribution to research). Furthermore, there is a long recognized positive effect due to simply engaging in any

therapeutic interaction (e.g. Fourie, 2009). However, it is unlikely that the TFI intervention specifically was responsible for this positive change

Conclusions regarding outcomes

In summary, I found that A-TDCS had a specific effect on reducing the overt speech impairment in developmental stuttering, rather than the psycho-social impact of the disorder. The additional speech measures reported in appendix 4 were also consistent with these main findings (A-TDCS increased phonemic fluency but did not affect measures of anxiety or communication attitude). Current Speech and Language Therapy practice for adults who stutter (at least in the UK) has shifted focus away from directly targeting speech disfluency. One reason for this shift is the particular difficulty achieving long-term changes in the core speech impairment of stuttering. These findings establish a direction for future research to improve outcomes regarding the core speech impairment of developmental stuttering, which could be combined in clinical intervention with established methods for reducing the negative impact of living with the condition.

4.5.2 Exploratory analyses

A-TDCS reduced disfluency during intervention, with differing effects on reading and conversation

In addition to my main research questions, I was also interested in how A-TDCS interacted with the TFI behavioural techniques over the course of the intervention. During reading, A-TDCS induced a decrease in disfluency, relative to baseline levels, which did not significantly vary across days. Within-session reductions in fluency decreased over successive sessions, however this was balanced by increased

retention of fluency between sessions in the A-TDCS group, giving rise to an overall stable effect. During the conversation task, however, the effect of A-TDCS was not evident in all sessions, but increased over successive sessions resulting in a significant group difference by the end of the intervention. The changes in fluency seen for the two tasks significantly differed across the intervention, although this effect was not modulated by A-TDCS. Importantly, the effect of the intervention, measured post TFI on the final session, was reduced disfluency during both speaking tasks for the A-TDCS group compared with the sham group (who showed no change from baseline).

The immediate and stable fluency improvement seen during reading does not follow a typical pattern of cumulative TDCS-modulated improvements reported in previous mutiple-session studies of motor learning (e.g. Reis 2009, Reis 2015). It is an interesting possibility that the large gains in early sessions reflect an interaction between A-TDCS and the immediate fluency induced by TFI, i.e. A-TDCS modulation appeared early due to an immediate rather than gradual benefit of the behavioural intervention. Alternatively, effects in the early sessions may have been more influenced by other random factors, and so a less reliable than the later effects (although, variance in the A-TDCS group was not larger in the early sessions). A better understanding of the neural mechanisms involved in TFI, and how A-TDCS may act on these mechanisms, would be helpful for informing further work on using this combination in therapeutic intervention. This issue is discussed further in section 5.2.3, and in the general discussion.

The effects of A-TDCS on conversation were cumulative, which was consistent with our predictions and with previous motor learning multi-session studies. Conversation is a more habitual speaking task than reading aloud, and cognitive/linguistic strategies for avoiding overt stuttered moments are often used. The effects of A-TDCS may take longer to emerge from the 'noise' of these various other factors influencing speech, compared to reading aloud during which fewer strategies can be used to mask the underlying speech-motor disorder. The stable benefits of A-TDCS during reading over the course of the intervention were associated with more persistent fluency increases at follow-up. This would suggest that a longer intervention period, to produce a more stable effect of A-TDCS, on conversation immediately following each TFI session (e.g. significant group differences over several consecutive days), could result in longer-lasting effects on fluency during conversation.

One of the several reasons for including both a reading and a conversation task in the trial was the recognized inter-individual variability in symptoms across speaking tasks. In the single-session study, the majority of participants (12 out of 16) stuttered more during reading than conversation. However, here we found the direction of this difference was more balanced (16 out of 30 participants stuttered more during reading). Since we recruited participants with more severe symptoms for the current study, this raises interesting questions about the relationship between severity and stuttering symptom profile. It would also be interesting to interrogate the data further regarding possible differences in responsivity to A-TDCS according to individual symptom profile, although our sample size precludes a detailed examination of this question.

A-TDCS did not have significantly different effects on stutters compared to other disfluencies

I included a wider range of disfluencies in the RCT than I measured in the feasibility study. In addition to the core speech characteristics of stuttering, I also counted other disfluencies that have been associated with secondary, avoidance behaviours. I found no significant difference between reductions in stutters and in other disfluency types during or following the intervention. This is encouraging for treating stuttering. It is possible that targeting left IFC was important for a general effect on fluency, as disfluencies involving avoidance of words may have involved linguistic rather than motor planning processes, and left IFC function is important for both processes. This hypothesis could be tested by comparing TDCS protocols targeting IFC with those targeting articulatory M1 (which would be hypothesised to have a more focused effect on core characteristics associated with impaired motor planning and execution), using high-definition TDCS protocol, and neuro-navigation.

Other limitations and considerations

As this was the first RCT investigating the effects of TDCS in developmental stuttering, and based on the findings of our feasibility study, I chose restrictive eligibility criteria to increase sensitivity to A-TDCS. Now that I have shown benefits of using A-TDCS in male, right-handed adults who stutter with at least moderate severity, it will be important to test effects on a more varied group of adults who stutter. This will help to establish the clinical scope of the approach, and any systematic differences in effect may also help us to better understand the mechanisms involved in TDCS and in developmental stuttering.

Although participants were randomly allocated to the arms of the trial, the A-TDCS group had more severe symptoms on average, and greater within group variance. Although the baseline difference in symptoms was not significant, it would have been preferable to minimise any difference by using stratified randomization. However, this would necessitate completion of the recruitment phase prior to group allocation and trial commencement. Such an approach was not possible for this trial, as it took over one year to recruit an eligible sample. Recruitment and intervention phases were run in parallel in order that the trial could be completed within the funding time frame. The difference in severity between groups would have possibly presented a problem, if we expected some fluency improvement in both groups, because the A-TDCS group had more room for improvement. However, I hypothesized that the sham group would not change from baseline, which avoided this issue, and this hypothesis was supported. Furthermore, exclusion of the participant in the A-TDCS group with extremely outlying data at baseline did not affect the results.

I used TFI methods, as the priority was an intervention that would result in immediate and near to complete fluency in all participants, and I achieved this result. One reason for this choice was that I wanted to minimize stuttering during A-TDCS, to avoid reinforcing it. This was similar to an error-free learning approach (Evans et al., 2000), which has been used in the treatment of speech and language disorders (Fillingham, Sage & Lambon Ralph, 2006). However, TDCS studies with clinical populations have generally used stimulation in combination with training in which errors are not minimised, and the outcomes of such interventions have been successful. Within the motor cortex, TDCS is thought to act by the same plasticity-inducing mechanism as motor learning, and the interaction between the two is

important for long-term effects (Stagg et al., 2011a). However, as TFI appears not produce a learning effect alone, it is not clear how TDCS interacts with TFI to support persisting fluency. Possibly, larger fluency benefit would be achieved by pairing A-TDCS with a behavioural approach that itself leads to persistent fluency gains (such as fluency-shaping therapy). However, it is equally possible that the effortless immediate fluency achieved by TFI methods, or the neural mechanisms underlying it, could be critical to the outcomes achieved here. Analysis of the MRI data collected as part of this trial will be an important next step in understanding the neural correlates of these behavioural effects (as discussed in chapter 5).

A related issue is the effect of the particular TFI methods used. I chose a combination of choral speech and metronome-timed speech to achieve a high level of fluency in all participants, whilst also increasing ecological validity and task variety, to support engagement in the intervention. Both techniques increase auditory input regarding speech, which may aid sensorimotor integration, and also provide external timing cues. However, they have some differing effects on brain function. Increases in the activation of auditory cortex and left IFC are seen during both TFI techniques (Fox et al., 1996; Toyomura et al., 2011) but the effects on SMA and basal ganglia vary (Fox et al., 1996; Giraud et al., 2008; Toyomura et al., 2011; Toyomura et al., 2015). Interpretation these differences is hampered by discrepancies between these studies, in the pattern of activation reported during normal speech conditions in adults who stutter (e.g. underactivity in basal ganglia nuclei (Toyomura et al., 2011) vs overactivity (Fox et al., 1996; Giraud et al., 2008), which could reflect methodological differences or subtypes of developmental stuttering. However, the differences between the TFI methods are important to bear in mind, particularly if they

differentiate between 'normalisation' of brain networks for fluent speech compared to compensatory activations. As all participants in the current study used both techniques, it is not possible to compare effectiveness of the methods in combination with A-TDCS. However, this is an interesting direction for further research. It is an open question whether normalisation of the impaired brain circuit for fluent speech, or a robust, lasting compensation for this impairment, is the more achievable or effective outcome for a TDCS intervention.

4.5.3 Conclusion

This RCT demonstrated, for the first time, that A-TDCS can increase speech fluency in adults who stutter. I found significant reduction in the frequency and severity of stuttering symptoms, which persisted for at least 5 weeks following a 5-day intervention. Both the disfluencies that form the core characteristics of developmental stuttering, and secondary characteristics associated with maladaptive avoidance strategies, were reduced. This study indicates the clinical potential of TDCS in the treatment of developmental stuttering. Further work should investigate the optimal TDCS parameters for increasing fluency and options for translation into clinical practice.

Chapter 5

General Discussion

5.1 Summary of main findings

The aim of this thesis was to investigate how A-TDCS can be used to increase speech fluency, with a particular focus on the potential application to developmental stuttering. First, using a series of three single-session experiments in typically fluent speakers, I found that applying A-TDCS over left IFC increased speech motor learning, compared to sham, but did not affect consolidation of this learning. The experiments compared the effects of different stimulation intensities and configurations. As there were no additional benefits from increasing stimulation intensity, or using a bi-hemispheric configuration, I went on to use 1 mA uni-hemispheric stimulation over left IFC in the following studies, with adults who stutter. The feasibility of using A-TDCS to increase fluency in adults who stutter was tested with a single session of stimulation in combination with a choral speech task. I did not find any significant effect of A-TDCS, however, a trend towards stuttering reduction gave some indication that fluency might be increased using a mutiple-session approach. Consideration of the methodological issues in this study, which likely reduced sensitivity to detect the effects of A-TDCS, was important to inform the design of the subsequent RCT in adults who stutter. In the RCT, I found that 5 consecutive sessions of A-TDCS over left IFC, in combination with TFI behavioural techniques, significantly reduced disfluency for at least 5 weeks following intervention. A-TDCS specifically modulated the speech impairment of developmental stuttering, i.e. core and secondary speech disfluencies were reduced, but not the psycho-social aspects of the condition.

The studies contributing to this thesis raised a number of interesting issues, which should be considered in future work aimed at modulating speech fluency using TDCS. These issues are discussed in the following sections.

5.2 Issues regarding single-session TDCS studies

The single-session studies in this thesis indicated that A-TDCS can improve speech fluency. However, the effects we found were weak, i.e. a significant difference was only found by pooling the three experiments in chapter 2, and I found only non-significant trends towards fluency benefits in chapter 3. It is likely that individual variability in response to A-TDCS was an issue in these studies. Variability in inter- and intra-individual in the physiological and the behavioural response to TDCS is well documented (Horvath et al., 2015; Krause et al., 2014; Wiethoff et al., 2014; Bestmann et al., 2015). Conducting single-session studies, in which only behavioural measures are taken, seems particularly vulnerable to variability obscuring effects of TDCS. However, embarking on multiple-session TDCS studies, especially with clinical populations, is a considerable investment with an increased risk of failure in the absence of any preliminary investigation of potential effects. Several possible approaches have been suggested to gain more useful information from single-session TDCS studies.

The assumptions of many TDCS studies, including those reported here, are based on over-simplifications of the physiological mechanisms of TDCS, and how these physiological effects influence behavior. For example, I have assumed that the net effect of A-TDCS is excitation of the underlying cortex. However, the current flow will affect cells differently depending on their depth and position within gyri or sulci (Miranda et al., 2013; Rahman et al., 2013) and the maximal current density will not

necessarily occur in the cortex underlying the electrode of interest. The net effect on cell polarization, then, would be expected to vary with individual differences in anatomy. Applying computational models to estimate the current flow would allow stimulation to be applied more uniformly across individuals (Bikson, Rahman & Datta, 2012). In addition, current flow could be influenced by using a high-definition configuration, to focus and contain it within one cortical region, or using a large return electrode, to decrease current density underlying that location.

However, even if we could apply current more precisely, this is of limited use without a better understanding of the relationship between TDCS effects at the physiological and behavioural levels. The use of computation neurostimulation in TDCS has been suggested to aid bridging between the levels (Bestmann et al., 2015), following models used to understand the effects of TMS (e.g. Husain et al., 2002) and deep brain stimulation (e.g. McIntyre & Foutz, 2013). Combining TDCS with neuro-imaging has also proved useful: concurrent fMRI has revealed changes in activation and connectivity within the naming network, associated with A-TDCS over left IFC (Holland et al., 2011; Holland et al., 2016). I collected a range of MRI measures prior to, and one week following, intervention as part of the randomised controlled trial, however, I was not able to incorporate MRI into the single-session studies. In future, online and offline combination of fMRI with single-session TDCS will be considered, to elucidate the mechanism of TDCS on speech motor control. Furthermore, it is also an option to combine TDCS with single- or paired-pulse TMS, to relate changes in motor system excitability and connectivity, and their variation between individuals, to changes in speech behavior.

5.3 Relating TDCS effects in normally fluent speakers to people who stutter

I undertook the experiments described in chapter 2 as a proof-of-principle that A-TDCS could be used to modulate speech motor learning, prior to commencing the studies with adults who stutter. However, extrapolating from effects in an intact speech motor system, to a system with abnormalities at various loci, has obvious problems. For example, I found no significant additional benefit of using bi-hemispheric, compared to uni-hemispheric, stimulation on speech motor learning (and a questionable effect on generalisation) in typical adults. Studies in typical adults do not consistently show a behavioural effect of C-TDCS, and it could be the case that a small inhibitory effect can easily be compensated by the activity of a normally functioning brain (Galea et al., 2009; Vines et al., 2008). However, when the balance of neural activation is altered, for example in aphasia where over-activation in the spared hemisphere can inhibit recovery, bi-hemispheric TDCS can be a useful method for 're-balancing' (Lindenberg et al., 2010; Bolognini et al., 2011; Marangolo et al., 2016). Altered lateralisation within the speech motor network is consistently reported in developmental stuttering, and it is not yet clear which right hemisphere activations may be compensatory, maladaptive or part of the primary pathology. Therefore, bi-hemispheric stimulation over IFC in adults who stutter remains an interesting line of investigation. In fact, combined with neuro-imaging, this may further our understanding the neural mechanisms of stuttering, as well as developing possibilities for the therapeutic modulation of fluency.

5.4 Exploring TDCS as an adjunctive therapy in developmental stuttering

5.4.1 How does A-TDCS over left IFC affect the brain networks for fluency?

The randomised controlled trial, described in chapter 4, demonstrated a robust behavioural effect of A-TDCS on decreasing disfluency, lasting for at least 5 weeks. The results offer significant promise for the future application of noninvasive stimulation as an adjunctive therapy for adults who stutter. The change in fluency could be associated with numerous changes in the speech motor network, within the IFC, and in connected regions. The next important step will be to analyse the MRI measures taken before, and one week following the intervention, which include fMRI during speech, and at rest, DTI, and MR spectroscopy.

Various underactive loci in the left IFC have been described as important in the aetiology of developmental stuttering, and there is inconsistency regarding whether these under-activations can be reversed by therapy. For example, an increase in activation in the left rolandic operculum (overlying, or close to, the site of consistent white matter disruption: Sommer et al., 2002; Chang et al., 2008; Watkins et al., 2008) was reported twelve weeks following an intensive course of fluency-shaping therapy (Neumann et al., 2005), and argued as critical to successful therapeutic outcome. However, reduced functional connectivity at rest in left BA44 (Lu et al., 2012) has been described as important in the aetiology of the disorder, associated with structural anomalies, and shown to be resistant to therapeutic plasticity. If left IFC under-activity is particularly resistant to change from behavioural techniques alone, and plasticity with this region is important for lasting fluency, TDCS could provide an

external means of promoting this plasticity. Analysis of the speech task fMRI, and resting-state fMRI measures taken during the RCT will be useful first steps in examining this possibility.

Neurocomputational models of developmental stuttering have more generally implicated abnormal connectivity between the ventral premotor cortex, basal ganglia and thalamus (Civier et al., 2010; Civier et al., 2013). Interestingly, functional coupling within the cortico-striato-thalamo-cortical network has been modulated by TDCS over the motor cortex (Polania, Paulus & Nitsche, 2012). Furthermore, application of TDCS over M1 also reduces motor impairments in Parkinson's disease (Broeder et al., 2015), which suggests that this approach can promote plasticity within an impaired cortico-striato-thalamo-cortical network. If a basal ganglia impairment, rather than a cortical one, is the critical pathology in developmental stuttering, acting on connected frontal cortical regions with TDCS could still be an effective therapeutic approach.

5.4.2 Could A-TDCS combined with TFI have particular fluency benefits?

In the discussion section of chapter 4, I briefly considered the issue of how A-TDCS may interact with the behavioural tasks used in the RCT, and how future studies should consider the relative benefits of fluency-shaping therapies versus TFI, in combination with TDCS. I revisit this issue here, to focus on a feature of TFI techniques that may lend them particular promise for lasting fluency improvement in combination with TDCS.

I combined A-TDCS with TFI methods in the studies with adults who stutter, primarily because these behavioural techniques have a consistent and immediate effect of increasing fluency. However, I did not make any specific predictions regarding how A-TDCS would interact with a particular network engaged during TFI. This behavioural approach was successful in terms of increasing fluency, and interacted effectively with A-TDCS. However, it is important to consider, when taking the next steps in applying A-TDCS in developmental stuttering, that short-term changes in fluency are not uncommon, but long-term maintenance is a long-standing difficulty. Choice of behavioural technique may prove critical to promotion of lasting fluency.

The more posterior sections of the left IFC have been described as particularly important for the automatisation of fluent speech, and abnormalities in this region implicate an impaired speech automatisation process in developmental stuttering (e.g. Neef et al., 2016). Fluency therapy approaches likely work by engaging compensatory networks, through effortful practice of new speaking patterns (and so de-automatisation: Alm, 2004). However, relapse of stuttering symptoms after fluency-shaping therapy is a relatively common occurrence (Craig & Hancock, 1995). The lack of persistence of therapy effects might be related to an impairment in posterior IFC limiting the transition to automaticity of new, fluent, speech patterns.

In contrast to fluency therapy, which involves explicit practice of novel speaking patterns, TFI methods – particularly choral speech and altered sensory feedback – are notable for their spontaneous, effortless effect. However, the clinical utility of TFI methods has been limited, to date, by the lack of fluency carry-over. Choral speech,

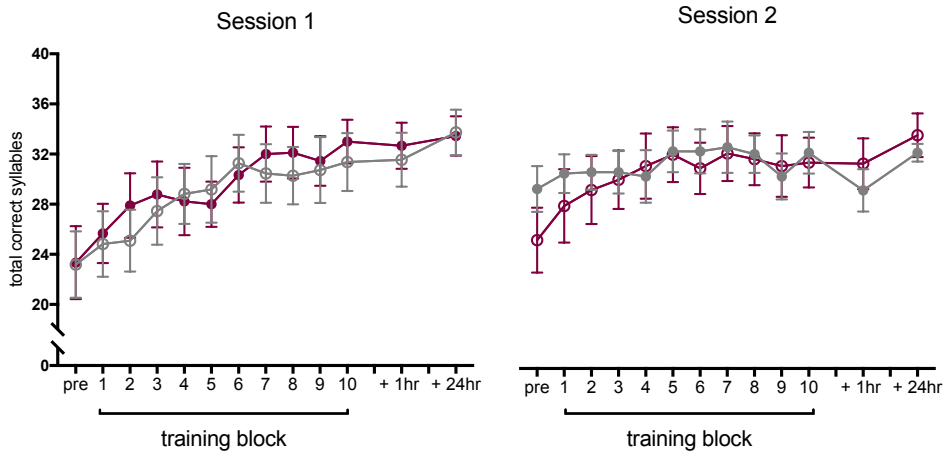
one of the TFI methods used in this thesis, promotes neural activation consistent with engagement of a network for highly automated speech, including increasing left BA44 activity (Fox et al., 1996). Metronome-timed speech, the other TFI method used here, is a more explicit technique for enhancing fluency, and has been associated with engagement of compensatory neural mechanisms (Alm, 2004). However, effort decreases and the sensation of a spontaneous entrainment to the external signal increases, as the metronome rate matches more closely to natural speech rate. Metronome-timed speech at a natural speaking rate also increases activation in left BA44 (Toyomura et al., 2011). It is an interesting possibility that TFI could be used to temporarily engage a network for automatic, fluent speech, and that TDCS could promote plasticity in this network to support long-lasting, effortless fluency. Further work should compare the effects (on fluency and neural connectivity) of adjunctive TDCS, with TFI tasks varying in degree of spontaneity of fluency induction, and with fluency therapy using explicit practice. Extended follow-up of these changes will be important for understanding how positive long-term fluency outcomes can be supported.

5.5 Conclusion

The studies in this thesis demonstrate that applying A-TDCS over left IFC, a cortical hub for speech planning and sensorimotor integration, can increase speech motor skill in typical speakers, and enhance speech fluency in adults who stutter. The randomised controlled trial of A-TDCS in combination with temporary fluency inducing techniques is the first demonstration of the potential of TDCS to improve treatment for developmental stuttering.

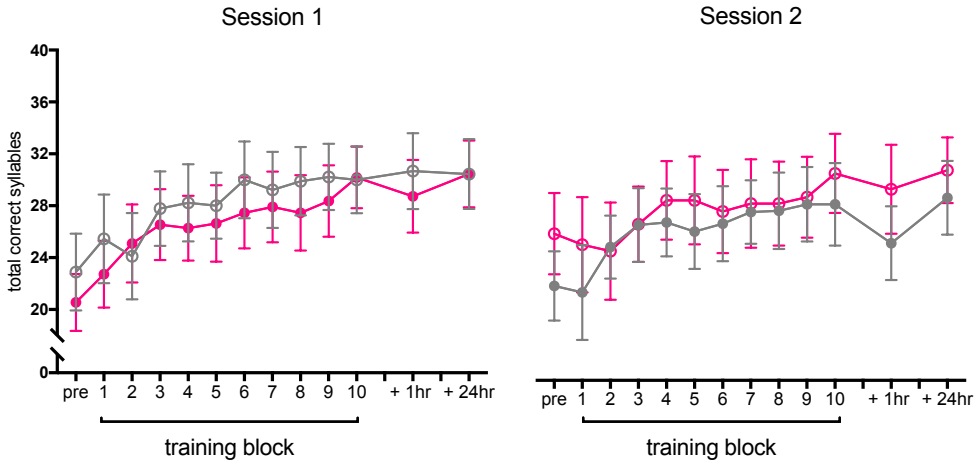
Appendices

Appendix 1: Nonword learning study



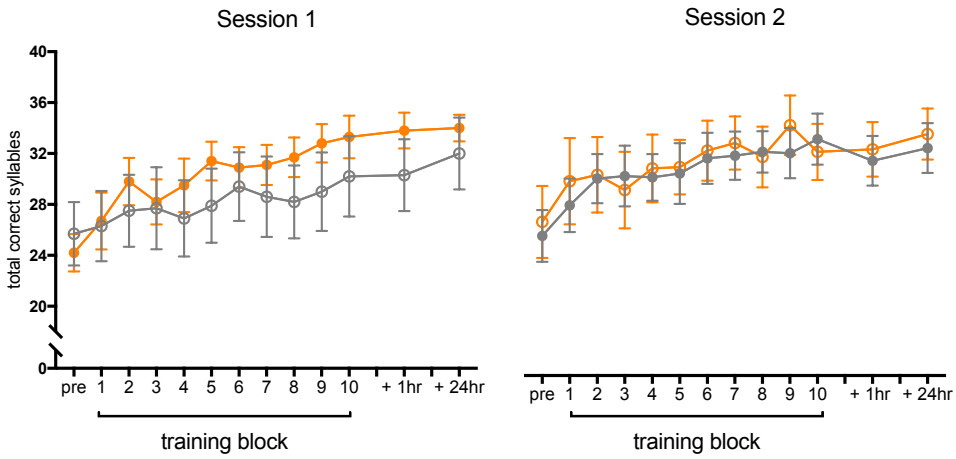
The mean total number of correctly repeated syllables is plotted at baseline, during each training block, and 1 and 24 hours after training, for the 1 mA RSOR (dark pink) and sham (grey) groups. Filled circles and open circles denote the two groups receiving A-TDCS in different orders (filled = A-TDCS in session 1, open = A-TDCS in session 2). Error bars show s.e.m.

Figure A1: Effect of 1 mA A-TDCS (RSOR) vs sham on nonword repetition during and following training in both sessions



The mean total number of correctly repeated syllables is plotted at baseline, during each training block, and 1 and 24 hours after training, for the 2 mA RSOR (light pink) and sham (grey) groups. Filled circles and open circles denote the two groups receiving A-TDCS in different orders (filled = A-TDCS in session 1, open = A-TDCS in session 2). Error bars show s.e.m.

Figure A2: Effect of 2 mA A-TDCS (RSOR) vs sham on nonword repetition during and following training in both sessions



The mean total number of correctly repeated syllables is plotted at baseline, during each training block, and 1 and 24 hours after training, for the 1 mA RSOR (dark pink) and sham (grey) groups. Filled circles and open circles denote the two groups receiving A-TDCS in different orders (filled = A-TDCS in session 1, open = A-TDCS in session 2). Error bars show s.e.m.

Figure A3: Effect of 2 mA A-TDCS (RSOR) vs sham on nonword repetition during and following training in both sessions

Appendix 2: Randomised controlled trial - Consort 2010 Flow Diagram

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

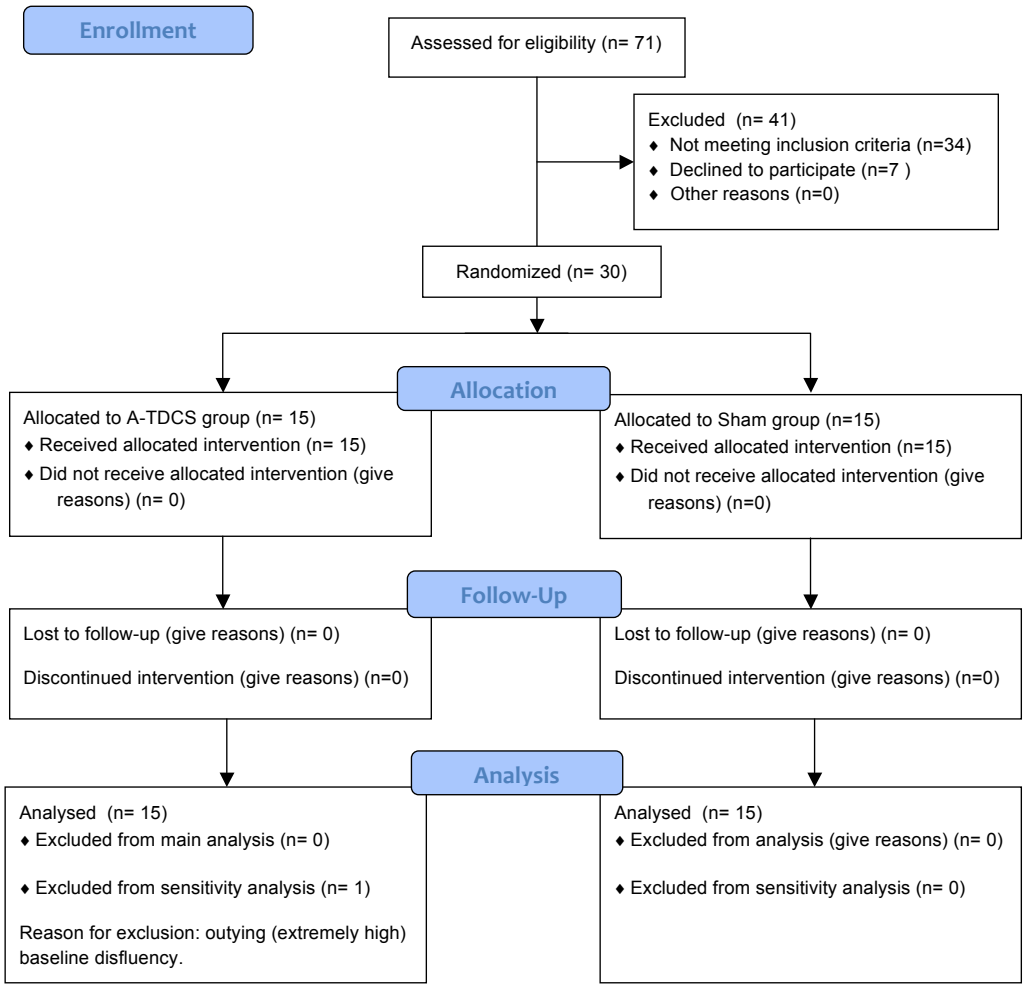


Figure A4: CONSORT flow diagram

Appendix 3: Randomised controlled trial - Response to TFI tasks

I assessed response to the TFI tasks to ensure that any group differences in outcomes could not be attributable to different levels of engagement in, or effectiveness of, the TFI tasks.

Table A1 shows disfluency and task proficiency during the TFI tasks across the course of the intervention. I tested for any group differences in disfluency during the TFI tasks, using a series of Mann-Whitney tests. Disfluency was very low for both groups during TFI on all days (equivalent to no greater than 'borderline' stuttering). Disfluency did not differ between the groups on days 1 to 4; however, on day 5 it was significantly lower for the sham group than the A-TDCS group ($U = 62$, $p = .037$). I also compared task proficiency between groups using a series of Mann-Whitney tests. Both groups showed a median level of performance corresponding to between good and excellent proficiency on each day, and there were no significant differences between the groups on any day.

In summary, both groups responded well to the TFI intervention, with very minimal difference between the groups. The only significant difference was during the final session, where the sham group disfluency was lower than the A-TDCS group during the TFI task (it should be noted that, post TFI in this session the A-TDCS showed significant reduction of disfluency relative to sham). Therefore, I can conclude that the positive outcomes of this trial - reduced frequency and severity of disfluency following A-TDCS combined with TFI - were not due to the A-TDCS showing a stronger response to TFI.

Table A1: Disfluency and task proficiency during TFI tasks

	Intervention session				
	1	**2**	**3**	**4**	**5**
% ds					
A-TDCS	1.56 (1.37)	1.60 (1.36)	1.36 (1.61)	1.26 (1.93)	1.46 (1.31)
Sham	0.80 (1.96)	0.53 (1.43)	0.60 (1.10)	0.58 (0.91)	0.31 (1.50)
Task proficiency					
A-TDCS	1.50 (1.50)	1.50 (0.75)	1.25 (0.50)	1.25 (0.75)	1.25 (0.50)
Sham	1.75 (1.50)	1.25 (0.75)	1.50 (1.00)	1.25 (1.00)	1.25 (0.50)

Cells show group medians, with interquartile range in parentheses. Task proficiency was rated on a 5-point Likert scale, with 1 corresponding to excellent.

Appendix 4: Randomised controlled trial - Assessment of potential harms of the intervention

Reduced speech naturalness, or adverse reactions to application of A-TDCS were considered potential 'harms' of the intervention. Therefore, I monitored these factors throughout the intervention, and report them here, in accordance with CONSORT 2010 reporting guidelines.

I used a questionnaire developed by Brunoni and colleagues (Brunoni et al., 2011) to monitor adverse effects of A-TDCS (figure A5). Due to researcher error, two participants (both in the sham group) were not requested to complete these questionnaires. Severity responses for the remaining 28 participants were coded on a four-point scale, with zero corresponding to 'absent' and three corresponding to 'severe', and the mean response for all items was calculated for each session. Participants in both groups reported some adverse effects during intervention (most commonly, itching or tingling under the electrodes). The mean ratings for each group across the 5 sessions fell between 'absent' and 'mild' (see table A2). I entered the mean ratings for each session into a mixed model ANOVA with group as the between-subjects factor (A-TDCS, sham) and intervention session as the within-subjects factor (1 to 5). There was a significant main effect of session, with a linear trend towards lower scores as intervention progressed ($F_{4,104} = 2.79$, $p = .030$; planned linear contrast, $F_{1, 26} = 6.46$, $p = .017$). This suggests that participants in both groups became less sensitive to the sensations associated with stimulation, with repeated application of real or sham stimulation. There was no significant main effect of stimulation group

($F_{1,26} = 2.76$, ns) or interaction between stimulation group and session ($F_{4,104} < 1$), indicating that A-TDCS did not induce more adverse effects than sham stimulation.

Did you experience any of the following during the session? (please tick)					If **yes,** how strongly do you think it was related to tDCS? (please tick)				
	absent	mild	moderate	severe	Not at all	remotely	possibly	probably	definitely
Headache									
Neck pain									
Scalp pain									
Tingling									
Itching									
Burning sensation									
Skin redness									
Sleepiness									
Trouble concentrating									
Acute mood change									
Others(please specify)									

Figure A5: TDCS adverse effects questionnaire, from Brunoni, 2011

Table A2: Mean TDCS adverse effects ratings

	Intervention session				
	1	**2**	**3**	**4**	**5**
A-TDCS	0.29 (0.04)	0.29 (0.04)	0.28 (0.05)	0.24 (0.04)	0.22 (0.05)
Sham	0.20 (0.04)	0.17 (0.05)	0.19 (0.06)	0.16 (0.05)	0.12 (0.05)

Cells show mean ratings, with s.e.m. in parentheses. Ratings were on a scale ranging from 0 to 3, with 0 corresponding to absent, and 3 corresponding to severe.

I assessed speech naturalness for every speech sample, using a nine-point scale with 1 corresponding to highly natural sounding speech. Mean naturalness ratings for both groups fell around the midpoint of the scale at baseline and follow-up (see table A3). To test whether A-TDCS affected speech naturalness following intervention, I entered the mean naturalness rating for the two speaking tasks into a mixed model ANOVA with group as the between-subjects factor (A-TDCS, sham) and time point as the within-subjects factor (baseline, + 1 week, + 5 weeks). There was no significant main effect of stimulation group ($F_{1,28} < 1$), time point ($F_{2,56} = 2.61$, ns), or interaction between these factors ($F_{2,56} = 1.08$, ns), indicating that neither A-TDCS nor the behavioural intervention alone (sham group) reduced speech naturalness.

Table A3: Mean speech naturalness ratings

	Time point		
	Baseline	**+ 1 week**	**+ 5 weeks**
A-TDCS	5.63 (0.44)	5.10 (0.43)	4.97 (0.43)
Sham	5.55 (0.44)	5.50 (0.43)	5.37 (0.43)

Cells show mean ratings, with s.e.m. in parentheses. Ratings were on a scale ranging from 1 to 9, with 1 corresponding to highly natural sounding speech, and 9 to highly unnatural sounding speech.

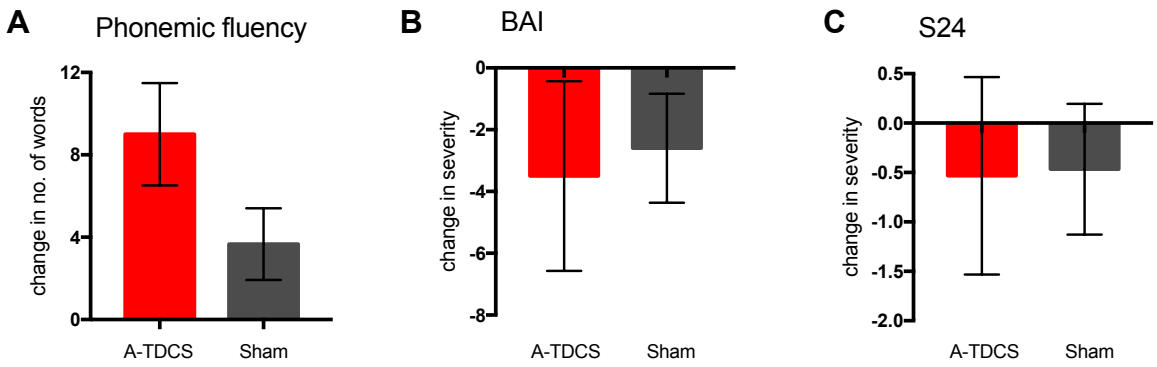
In summary, no significant harms were associated with the intervention, either related to TFI or to A-TDCS. Furthermore, blinding to stimulation condition during intervention was effective.

Appendix 5: Randomised controlled trial - Additional measures of speech and psycho-social impact of stuttering

In addition to the primary and secondary outcome measures of the randomised controlled trial, I also assessed phonemic verbal fluency, anxiety and attitude to communication. The main reason for including these assessments was to check that the groups were well matched on a range of characteristics relevant to developmental stuttering. I reported baseline performance on these additional measures in chapter 4, and confirmed that the groups were well matched.

I also re-administered all assessments at 5-week follow-up, to test whether the effects A-TDCS were also seen on these measures. Figure A6 shows change, relative to baseline, in phonemic fluency (A), anxiety (B. Beck Anxiety inventory: BAI) and communication attitude (C. S24 scale). Independent samples t-tests revealed no significant difference between the groups on the BAI or S-24 measure. However, phonemic fluency improved significantly more in the A-TDCS group than the sham group, ($t_{28} = 1.76$, $p = .04$, one-tailed).

In summary, the pattern across these additional measures is consistent with the primary and secondary trial outcomes - A-TDCS significantly improved speech fluency impairment, but did not affect the negative psycho-social consequences of this impairment.



Mean change, relative to baseline, is plotted for the A-TDCS (red) and sham (grey) groups, with error bars showing s.e.m. Panel A shows change in phonemic fluency, B shows change in BAI severity score, and C shows change in S24.

Figure A6: Change in additional measures 5 weeks following intervention

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