# Neural and Psychological Correlates of Stuttering




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*This thesis is humbly dedicated to the honourable memory of*

*Dominic Barker and Helen Barker.*

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# Preface

The data presented in Chapters 2 and 3 of this thesis were collected by Professor Watkins' research group in previous years at the University Oxford and subsequently inherited. The data in Chapters 4 and 5 were collected by me.

Chapter 3 has been published in the journal Brain Communications. Chapter 4 has been pre-registered and accepted for publication in the journal Neurobiology of Language.

# Abstract

Stuttering presents a fascinating paradox: fluent in thought, yet disruptions in speech. Even more intriguing, people who stutter (PWS) may articulate complex ideas with complete fluency when there is no communicative intent, still may struggle to say their own name in public. My research examines the stuttering phenomenon in two stages: first, using functional MRI (fMRI) to find differences in brain activity associated with stuttering, and second, developing innovative techniques to provide options for people who want to work on their fluency.

In my first study, we examined brain activity differences between PWS and controls using data from four previous fMRI studies involving sentence repetition (109 participants in total). Despite this relatively large sample size, we found no significant group differences at a strict statistical threshold ($Z > 3.1$). However, a lower uncorrected threshold revealed results consistent with earlier meta-analyses, such as overactivity in the right anterior insular cortex, while our novel finding was the bilateral overactivation in the red nucleus of PWS. In the second study, we investigated the incomplete cerebral dominance theory by analysing data from the same fMRI studies in four different speech and language tasks. Our findings showed no support for this theory since language lateralisation did not differ between PWS and controls.

In the second part of my thesis, we evaluated the effectiveness of theta-gamma peak transcranial alternating current stimulation to enhance sensorimotor learning of speech in typically fluent speakers. While this protocol did not significantly impact speech adaptation in the learning phase, exploratory analysis suggested potential benefits in retaining the learned state during the after-effect phase. The final study introduced a creative use of choral speech (speaking in unison with another voice) to eliminate stuttering during presentations. The method led to a major drop in disfluent syllables, from 10% to below 3% on average, a level considered clinical threshold.

In the general discussion, I proposed a unified theory of stuttering that considers both neural and psychological correlates, along with future studies to develop interventions with the ultimate goal of enhancing speech fluency and reducing social anxiety in PWS.

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# 1

# Introduction

Communication is fundamental to human civilisation by making possible the complex exchange of thoughts, beliefs, and feelings. Language is central to this process, not merely as a cognitive tool for thinking but as an evolved mechanism primarily for communication (Fedorenko et al., 2024). Harari (2024) extended the role of language by suggesting that human communication adds an additional dimension to reality, one that transcends both objective (i.e., material objects) and subjective (i.e., individual feelings) realms. Through language, humans can create information networks based on abstract concepts, myths, and social constructs such as governments or currencies, which exist solely in collective imagination (Harari, 2024). This allows language to function as a powerful force in creating a civilisation, empowering us to communicate and collaborate in unprecedented ways.

One of the most remarkable features of human language is its generative capacity, known as recursion, which is a mathematical principle applied to linguistics (Chomsky, 1957). This allows humans to produce an infinite number of sentences from a finite set of words and syllables, making communication flexible and adaptable to any context. Speech is the primary function through which this linguistic ability is realised and allowed early humans to share stories, transmit knowledge, and coordinate actions, that are essential for forming social bonds. Lieberman (2013) argues that social connection is so essential to human survival that it could be considered as important as the physiological needs in Maslow's hierarchy (1943) as the ability to socialise is vital to securing other basic needs such as food, shelter, and safety. Therefore, speech also represents a means of survival, carrying with it the emotional weight of securing one's inclusion within social groups. This inherent pressure to speak fluently and effectively, or in a way that is considered acceptable and normal by societal standards, may stem from an evolutionary drive to

avoid neglect or rejection from our social tribes, where being excluded could threaten one's survival.

For fluent speakers, producing spoken language feels almost effortless, despite the complexity underlying the process. One striking example of this is the rapid pace at which speech is produced in ordinary conversations. English speakers, for instance, typically articulate two to three words, amounting to three to six syllables and ten to twelve phonemes, per second (Levelt, 1999). This remarkable speed is achieved through the precise and coordinated activation of dozens of muscles, including those involved in respiration, laryngeal function, and movements within the supralaryngeal vocal tract (Jürgens, 2002). Guenther (2016) provides a compelling perspective on the intricacy of this motor control:

> *"If we assume that each phoneme requires activation of one-tenth of these motor units and each motor unit requires only one command per phoneme, then we arrive at an estimate of 11,000 motor command signals that need to be generated in less than one second" (Guenther, 2016, p. 2).*

Despite this complexity and speed, fluent speakers make errors only once in every 500 to 1,000 words (Garnham, 1981). This high level of accuracy in speech production underscores our proficiency in verbal communication and the extensive neural mechanisms that support this uniquely human skill, which is perhaps the most complicated motor function used by any known living species.

Speech production involves transforming a phonological representation of an utterance into a series of articulatory motor commands. Research has shown that once a lexical item is selected, it is decomposed into smaller phonological units, such as syllables or phonemes, which must then be accurately sequenced (Cholin, 2011; Levelt & Wheeldon, 1994). This transformation is not merely a passive relay of information but involves complex neural computations to convert the abstract phonological code into motor commands that precisely control the movement of the vocal apparatus (Van Der Merwe, 2021). Given that this thesis focuses on stuttering, I will focus on the neural mechanisms underlying speech motor control, including the selection, coordination, and initiation of articulatory motor commands, and how these processes may differ in people who

stutter (PWS), rather than on the initial stages of speech formulation, such as lexical selection, or the later stages involving vocal tract muscles.

## 1.1. Neural correlates of speech production

Broca's model of speech production, developed in 1860s, was based on observations of patients with damage to the left inferior frontal gyrus, who experienced profound difficulties in producing fluent speech (Broca, 1861; Husain, 2024). In his seminal case study, Broca described a patient known as "Tan" (because "tan" was one of the few syllables he could articulate) who had significant speech production difficulties (Broca, 1861). He concluded that this region, in the posterior part of the frontal lobe, specifically left inferior frontal gyrus, now known as Broca's area, was critical for transforming the sounds of language (phonological representations) into precise motor commands that guide speech production (Hickok et al., 2023). While influential, this model has been increasingly questioned, as more research suggests a much more complex and interactive network of brain regions involved in speech production (for a critical review, see Husain, 2024).

Over a century after Broca developed his model, research has increasingly shown that Broca's area is not a uniform entity with a single function. Instead, it comprises multiple subregions, such as the pars opercularis (Brodmann Area 44) and pars triangularis (Brodmann Area 45) (Amunts et al., 1999; Conner et al., 2019; Fedorenko & Blank, 2020), which appeared to be engaged in different linguistic and cognitive tasks beyond articulation such as syntactic formation (Matchin & Hickok, 2020; Schell et al., 2017), word retrieval (Novick et al., 2005; Schell et al., 2017), and working memory (Buchsbaum & D'Esposito, 2008). Additionally, electrocorticography (ECoG) studies reported that neural activity in Broca's area primarily occurs before speech initiation, suggesting it is involved in speech preparation rather than in articulation itself (Castellucci et al., 2022; Flinker et al., 2015; Wang et al., 2021). Moreover, Penfield's early work demonstrated that surgical resection of Broca's area typically resulted in only transient speech deficits, implying that this region may not be as important for speech motor control as traditionally believed (Mohr

et al., 1978; Penfield, 1959). This is further supported by recent studies showing that patients undergoing resection of Broca's area generally experience minimal impact on fluent speech, while resections involving the precentral gyrus led to more pronounced articulation deficits (Chang et al., 2020; Rolston et al., 2015; Wilson et al., 2015). Additionally, direct electrical stimulation of Broca's area often induces naming deficits, or anomia, rather than disruptions in articulation (Chang et al., 2017; Lu et al., 2021; Penfield, 1959). Overall, the evidence suggests that Broca's area may play a more nuanced role, that contributes to higher-order aspects of language processing, such as syntactic integration and sentence-level production, rather than directly controlling speech movements (Chang et al., 2018; Matchin & Hickok, 2020; see also: Silva et al., 2022; Hickok et al., 2023; Husain, 2024 for more detailed discussion).

Unlike traditional models that describe speech production as a linear process, recent empirical results and theoretical frameworks emphasise the importance of precise sensorimotor integration, where feedback mechanisms continuously monitor and adjust speech movements (Guenther, 2016; Hickok et al., 2003; Houde & Jordan, 1998, 2002; Houde & Nagarajan, 2011; Tourville et al., 2008; Tourville & Guenther, 2011). This monitoring system includes two primary feedback control systems: auditory and somatosensory. These systems enable the speaker to make real-time adjustments to maintain accurate articulation, even in response to disruptions like speaking bite blocks such as holding a pencil between teeth (Baum et al., 1996; Hoole, 1987) or experiencing altered auditory feedback such as hearing one's own voice at a different pitch (Houde & Jordan, 1998; Tang et al., 2021). When the produced speech deviates from its intended target, errors are detected via these feedback control systems. For instance, an auditory error occurs if the actual sound output, indicated by formant values, does not match the desired acoustic targets encoded by auditory representations, while somatosensory errors arise when the expected tactile and proprioceptive sensations of speech movements differ from those experienced (Civier et al., 2010). Such feedback is essential for the dynamic regulation of articulation by facilitating real-time corrections. Disruptions in sensory feedback in typically fluent speakers, whether due to hearing loss (Cowie & Douglas-Cowie, 1992) or experimental manipulation of auditory input

(Yates, 1963), can compromise speech fluency and stability. This interaction between sensory and motor systems highlights the complexity of the neural networks involved in speech production, which include motor, auditory, and somatosensory regions, extending across both cortical and subcortical structures (Tourville et al., 2008).

### 1.1.1 A computational model of speech production: DIVA model

The DIVA (Directions Into Velocities of Articulators) model is a computational model providing a biologically informed framework for exploring how the brain learns and controls articulatory movements (Guenther, 1994; Guenther et al., 2006; Tourville & Guenther, 2011; Guenther, 2016). The model distinguishes between two main processes in speech production: feedforward and feedback control. The feedforward system is further subdivided into two components: an articulation circuit, which generates the precise muscle movements needed to produce speech sounds, and an initiation circuit, which supports these movements to occur at the correct time. This system allows for fluent speech in familiar situations by reading out the motor commands from memory. In contrast, the feedback system, which relies on auditory and somatosensory information, is essential for learning and fine-tuning speech. It enables the adjustment of speech in response to unexpected changes, such as speaking with an object in the mouth or encountering pitch disturbances in the acoustic output of speech (see Guenther, 2016 for more details).

According to the DIVA model, speech production begins with the activation of a "speech sound map" node, representing a phoneme, syllable, or sequence of syllables, located in the left ventral premotor cortex (vPMC) (Tourville & Guenther, 2011). This region primarily includes the anterior part of the ventral precentral gyrus. It is anatomically adjacent to the posterior inferior frontal gyrus (pars opercularis, also known as BA44) and the anterior superior insula. Once activated, this map triggers the primary motor cortex (M1) to execute the corresponding articulatory movements from memory, which is guided by the feedforward controller. Simultaneously, a copy of the motor command (known as the efference copy or corollary discharge proposed by Sperry, 1950 and von Holst & Mittelstaedt, 1950) is generated, to predict the expected auditory output of the speech sound. This predicted auditory signal is sent to the

auditory cortex, both directly (Makris et al., 2005; Matsumoto et al., 2004) and via the cerebellum (Blakemore et al., 2001). The feedback controller then compares this predicted sound with the actual acoustic output. If there is a discrepancy between the expected and actual sound, an error signal is generated, prompting corrective adjustments from the right premotor cortex (Tourville et al., 2008) and cerebellum (O'Reilly et al., 2008). This feedback mechanism trains the feedforward system over time, that will allow the model to produce accurate speech sounds (Purcell & Munhall, 2006).

The system refines its motor programs through repeated cycles of speech production and auditory feedback (Tourville & Guenther, 2011). Once these motor commands are well-learned, speech can be produced using only the feedforward controller (Guenther, 2016). As mentioned above, the efference copy generated by the feedforward controller, predicts the expected sensory feedback from the planned articulatory movements. This predictive mechanism allows speech to flow smoothly without needing to wait for real-time sensory feedback. If there is a mismatch between the predicted and actual sensory feedback, the system can quickly adjust the motor commands, even before the onset of articulation (Tourville & Guenther, 2011). While the feedforward controller processes the speech production, the feedback system remains on standby to step in if unexpected disruptions occur, such as unexpected noise or an accidental misarticulation (Tourville & Guenther, 2011). This dual control system provides both accuracy and adaptability in speech production.

### 1.1.2 Precentral gyrus

The precentral gyrus, located in the frontal lobe just anterior to the central sulcus, is important for generating the complex motor plans that the feedforward controller uses to execute precise movements of the vocal tract (Guenther, 2016; Hickok, 2012; Silva et al., 2022). This region is subdivided into the premotor cortex, situated in the lateral frontal lobe just anterior to the precentral gyrus, and M1, positioned within the anterior portion of the precentral gyrus itself. M1 is thought to display a precise somatotopic organisation, where different regions correspond to specific speech articulators (Dum & Strick, 2002; Penfield & Boldrey, 1937); however, it is worth

keeping in mind that this idea has been challenged by recent findings from Gordon et al. (2023), who proposed that M1 includes interspersed regions linked to a broader action control network, suggesting a more complex organisation involving both fine motor control and whole-body action planning. Regarding the speech articulators found in M1, the laryngeal area is found inferior to the hand region, followed by the lips and tongue, which are mapped progressively downwards and forwards along the gyrus (Bouchard et al., 2013). Further, a ventral laryngeal representation is located in the subcentral gyrus (Eichert et al., 2020). This detailed somatotopic arrangement allows M1 to activate specific musculature directly.

By applying non-invasive brain stimulation over left M1, several studies have assessed the role of speech motor adaptation in this region (Lametti et al., 2018; Scott et al., 2020; Tang et al., 2021). To investigate the causal role of M1 in the sensorimotor control of speech, a study applied low-frequency repetitive transcranial magnetic stimulation (rTMS) to temporarily disrupt activity in the tongue representation area of left M1 (Tang et al., 2021). During a syllable repetition task, participants experienced altered feedback with an increase in the first formant (F1) frequency while speaking. The authors reported that participants with disrupted tongue M1 activity failed to show the expected adaptation to the shift in the auditory feedback, whereas those in the control group, who received rTMS over the hand area in left M1, showed typical adaptive responses with decreased F1 and increased second formant (F2) frequencies. These findings suggest that the left ventral M1 plays a role in speech motor adaptation, complementing the DIVA model's focus on the cerebellum and right premotor cortex in adjusting motor commands based on auditory feedback.

### 1.1.3 Ventral premotor cortex

In the DIVA model, speech production starts with the activation of neurons in vPMC which is thought to be involved in converting phonological representations into precise articulatory commands (Tourville & Guenther, 2011). Evidence from other species supports its importance in the evolution of complicated vocal behaviours. For instance, in songbirds, the anterior vocal pathway, a cortical-striatal-thalamic loop connecting a human premotor cortex analogue to the

striatum and thalamus, is necessary for song learning and production (Chakraborty et al., 2017; Jarvis, 2019). Disrupting this pathway, such as through over-expression of a gene affecting this region's function, leads to stuttering-like behaviours in songbirds, suggesting that this circuit manages complex vocal sequences (Chakraborty et al., 2017). Similarly, in non-human primates, vPMC has been reported to coordinate facial movements, such as lip-smacking, which is thought to be a precursor to more sophisticated forms of communication (Shepherd & Freiwald, 2018).

There is strong evidence from neuroimaging and stimulation studies that vPMC is involved in speech production. fMRI research has consistently shown activation in the left vPMC during tasks involving syllable production (Bohland & Guenther, 2006; Eckers et al., 2013; Peeva et al., 2010; Riecker et al., 2008). For instance, Bohland and Guenther (2006) found that this region is more active when participants produce complex syllable sequences like "kla–tri–splu" compared with simpler ones such as "ka–ka–ka." Damage to vPMC often results in apraxia of speech, where people struggle to plan and coordinate the movements required for clear speech (Dronkers, 1996; Miller & Guenther, 2021). Studies using electrical stimulation and TMS provide evidence suggesting a causal role for this area in speech initiation, as temporarily disrupting activity here can make it difficult to begin speaking, as though the words are "stuck" (Ojemann et al., 1989; Stewart et al., 2001).

Reverse engineering, or decoding speech production from brain activity during attempted speech in patients with speech disabilities, provides valuable insights into the role of the left precentral gyrus. Guenther and colleagues (2009) pioneered this approach by implanting an electrode near the boundary between the left vPMC and M1 cortex in a 26-year-old man with locked-in syndrome. Neural signals detected by the implanted electrode were processed and routed to an artificial speech synthesiser. Over a 90-minute training session, the patient's performance in a simple vowel production task improved markedly, increasing from 45% accuracy in the first block to 70% in the last block. More recently, brain-computer interface technology has advanced to the point where sentences can be decoded from the left vPMC using microelectrode arrays, achieving classification accuracies of 92% for 33 orofacial movements, 62% for 39 phonemes, and 94% for

50 words (Willett et al., 2023). In contrast, decoding from pars opercularis (BA44) was far less successful, for instance, with word classification accuracy below 12%, which suggests that this region encodes minimal information about orofacial movements, phonemes, or words. Importantly, this evidence is consistent with the idea discussed above that the Broca's area is more involved in higher cognitive functions. Overall, the researchers concluded that the left vPMC contains a detailed representation of speech articulators, even within a small portion (3.2 x 3.2 $mm^2$), and that phonemic information remains intact even years after paralysis in people who can no longer speak intelligibly.

### 1.1.4 Dorsal precentral gyrus

While the evidence strongly showed the ventral portions of the precentral gyrus encodes articulatory motor commands, recent theoretical frameworks have suggested different roles for the dorsal regions of the precentral gyrus in speech production (Hickok et al., 2023; Silva et al., 2022). It has been argued that speech production involves dual pathways, with unique ventral and dorsal routes (Hickok et al., 2023), similar to the dual-stream model of speech perception proposed by Hickok and Poeppel (2000, 2004, 2007), or the two separate pathways of neural processing streams of vision identified by Mishkin and colleagues (1983). A recent review by Silva et and colleagues (2022) has hypothesised that the mid precentral gyrus (midPrCG), located between the cortical areas for hand and articulatory movements, plays a key role in coordinating motor aspects of speech, particularly in linking phonological processing with syllable-level motor execution. In their review, the authors emphasised that midPrCG helps connect the temporo-parietal regions with motor areas involved in speech (Fernández-Miranda et al., 2015; Glasser et al., 2016). Another hypothesis concerning the dorsal parts of the precentral gyrus came from Hickok and colleagues (2023), who proposed that a nearby region, involving the dorsal laryngeal motor area, is involved in coordinating vocal pitch. The evidence supporting this claim comes from a high-density intracranial recording study showing that this area is active in response to pitch accents during both speech and non-speech tasks, such as singing (Dichter et al., 2018). Together, these reviews and findings, suggest that different regions of the dorsal precentral gyrus

are specialised for different aspects of speech, mainly focusing on phonological sequences and pitch processing.

### 1.1.5 Cortico-basal ganglia-thalamo-cortical loop

The DIVA model describes the initiation circuit as essential for managing the timing and sequence of speech movements (Guenther, 2016). According to the model, the basal ganglia, especially the putamen (Booth et al., 2007), receive input from cortical areas involved in speech planning, such as premotor and motor cortices, to monitor ongoing movements and determine the timing of when to start or switch between motor commands. One of the key functions of basal ganglia is thought to filter out competing motor programs and select the proper one for execution (Bergman, 2021). This is achieved through the interaction of the direct and indirect pathways: the direct pathway promotes the desired motor command by reducing inhibitory signals to the thalamus, while the indirect pathway suppresses competing commands by increasing inhibition (Albin et al., 1989; Bergman, 2021). This balance supports selective activation of the intended motor sequence, such as the syllable “ba”, while suppressing competing alternatives such “bi” or “be” (Chang & Guenther, 2020). Then the basal ganglia outputs this processed information to the thalamus (Bergman, 2021; DeLong, 1990).

### 1.1.6 Supplementary motor area

SMA, positioned just in front of M1 on the medial surface, is the last stop of the cortico-basal ganglia-thalamo-cortical loop (Jonas, 1981; Ziegler et al., 1997). It receives input from the thalamus about the current state of the motor plan and then acts as a ‘temporal gatekeeper’, initiating each motor sequence at the precise moment (Chang & Guenther, 2020). For example, when a speaker produces the syllable “ba”, the basal ganglia monitor the articulators’ state and, once the “b” sound is complete, signal SMA to initiate the motor plan for “a” (Civier et al., 2013). Neurological evidence has supported the role of SMA in the initiation circuit by demonstrating that patients with lesions in this area experience speech arrest and involuntary vocalisations (Ackermann et al., 1996; Wieshmann et al., 2008). Additionally, direct stimulation of SMA can interrupt movement or trigger speech arrest and, in some cases, provoke involuntary movements,

vocalisations, or even a sensation of needing to speak (Fried et al., 1991; Penfield & Welch, 1951). For instance, Fried and colleagues (1991) found that stimulating SMA in epilepsy patients temporarily stopped their speech. However, recent evidence suggests speech arrest may be part of a wider inhibitory network, affecting not just speech but also other behaviours like music playing (Leonard et al., 2019) and gestures (Breshears et al., 2019) potentially involving pre-SMA and basal ganglia in a generalised stopping mechanism (Silva et al., 2022).

When the initiation of speech comes to an involuntary halt in real life settings, stuttering occurs. In the next section, I will introduce stuttering by discussing its incidence rate, epidemiology, symptoms, and its impact on people' lives. Following that, I will elaborate on the theoretical frameworks that explain both the neural and psychological correlates of stuttering.

## 1.2. Stuttering

Stuttering is identified by disruptions in the flow of speech, such as repetitions, prolongations, and blocks. Although PWS are fully aware of what they want to say, they experience difficulties in fluently articulating speech sounds. Affecting approximately 1% of the global population, or around 70 million people, stuttering occurs across nearly all cultures and languages (Van Riper, 1982). It typically emerges between the ages of 2 and 4, affecting about 3-8% of preschool-aged children, though around 75% of these cases resolve spontaneously (Yairi & Ambrose, 2013; Yaruss & Quesal, 2004). While developmental stuttering is the most common form, stuttering can also result from neurological incidents (referred to as neurogenic stuttering) such as stroke (Theys et al., 2013, 2024), traumatic brain injury (Theys et al., 2008), neurological disorders such as epilepsy (Sechi et al., 2006), neurodegenerative diseases like Parkinson's disease (PD) (Canter, 1971; Koller, 1983) or the recurrence of resolved childhood stuttering in the onset of PD (Burghaus et al., 2006b), or as a side effect of treatments of PD (Rusz et al., 2018) (see Craig-McQuaide et al., 2014 for a review). This thesis will focus on developmental stuttering, hereafter referred to simply as "stuttering".

Stuttering is more than just a disruption of speech fluency; it can profoundly affect the emotional well-being and social interactions of those who experience it. For example, children who stutter are more frequently targeted by bullies (Davis et al., 2002), enduring harassment such as name-calling, rumour-spreading, and gaslighting. Compared with their fluent peers, they are less likely to be seen as leaders and more often labelled as "bullied" or "seeking help" by their peers (Davis et al., 2002). Even in adulthood, PWS are often perceived as less intelligent (Ferguson et al., 2019), discriminated against in the labour market, and tend to have reduced earnings (Gerlach et al., 2018). The negative stereotypes surrounding stuttering can give rise to feelings of embarrassment, frustration, and low self-esteem. Therefore, it is not surprising that PWS are more prone to developing social anxiety disorder (Blumgart et al., 2010; Craig & Tran, 2014; Iverach & Rapee, 2014). Moreover, the fear of negative social evaluation related to stuttering may lead PWS to avoid social interactions (Peters & Starkweather, 1989), as they may perceive socialising as potentially harmful due to the stigma associated with stuttering (Iverach et al., 2009). This avoidance can hinder academic, professional, and personal opportunities, resulting in a cycle of isolation and reduced quality of life (Yaruss, 2010). Consequently, the combination of isolation and the weight of social anxiety create a higher risk for suicidal ideation among PWS (Tichenor et al., 2023). These psychosocial challenges that PWS encounter every single day, highlight the need and urgency for continued scientific research to better understand the underlying neurobiological and psychological mechanisms, and develop effective interventions.

Stuttering is one of the most common communication disorders, occurring far more often than conditions such as apraxia of speech, aphasia, or dystonia (National Institute on Deafness and Other Communication Disorders, 2024; Sommer et al., 2021; Yairi & Ambrose, 2013). Genetic factors play a role, with about 50% of PWS reporting a family history of the condition (Boyce et al., 2022). Twin studies reported high genetic influence for stuttering, with Rautakoski and colleagues (2012) attributing 82% of childhood stuttering variance to genetic factors and Dworznski and colleagues (2007) reporting heritability estimates between 58% and 66% in early childhood, while both studies found limited influence of shared environmental factors. Stuttering

is more prevalent in males than females, with a male-to-female ratio of about 4 to 1 in older children and adults (Craig et al., 2002), but near the onset of stuttering in pre-schoolers, this ratio is smaller, closer to 2 to 1 (Mansson, 2000). The precise neurodevelopmental mechanisms underlying these patterns remain unclear and warrant further investigation (Neef & Chang, 2024).

Stuttering often begins with whole-word repetitions, such as "apple apple apple," which are typically the first signs observed in young children, and a transition to part-word disfluencies (Howell, 2007). As the condition progresses, repetitions may shift to smaller speech units, including syllables and phonemes, as in "a-a-a-apple" and this transition has been suggested as an indicator of the persistence of stuttering (Conture Lesley, 1990; Van Riper, 1982). Over time, symptoms may advance to prolongations, where sounds are unintentionally stretched out, for example "ssssssounds", and blocks, where speech is halted such as "------blocks". In addition to the core symptoms, secondary behaviours develop through instrumental conditioning, where PWS associate physical concomitants like eye blinking, tongue biting, or head nodding with successfully getting the word out, even though these behaviours do not actually improve fluency (Guitar, 2018). The prominence of these behaviours can vary over time, with some becoming more pronounced at certain periods and others at different times.

Spontaneous recovery from stuttering, where the condition resolves without the need for a therapeutical intervention, is seen in approximately 75% of children who stutter (Yairi & Ambrose, 2013). Key factors influencing whether stuttering persists include family history, with children who have relatives who stutter being at higher risk, and male gender, as boys are more likely to stutter persistently than girls (Brown, 1945; Guitar, 2018). The age at which stuttering begins is also important, as a later onset, is correlated with a lower likelihood of recovery (Brown, 1945; Guitar, 2018). The type and severity of disfluencies are predictive as well, with more complex repetitions and prolonged stuttering episodes (e.g., "C-C-C-C-C-Charlie") projecting a higher risk of persistence compared with simpler forms (e.g., "C-Charlie") (Brown, 1945; Guitar, 2018).

It is worth noting that stuttering differs fundamentally from other speech disorders such as dysarthria, which involves a neuromuscular impairment affecting speech production, or apraxia of speech, where planning and sequencing of movements are disrupted (Chang & Guenther, 2020). In contrast, stuttering involves interruptions in the initiation of otherwise well-formed articulatory speech commands. It is still not clear as to whether stuttering is only related to speech motor functions or also to language proficiency (Katerina et al., 2011; Nippold, 2019; Smith et al., 2012) with some studies suggesting decreased (Shimada et al., 2018; Zaretsky et al., 2017) while another indicating slightly increased oral language skills in children who stutter (Watts et al., 2015).

## 1.3 Theoretical frameworks on the causes of stuttering

One of the significant challenges in identifying the neural correlates of stuttering and creating a reliable theoretical framework is the considerable variability in its manifestation, both within and between individuals (Constantino et al., 2016; Tichenor & Yaruss, 2021). There are significant individual differences in the manifestation of stuttering, with some people experiencing severe disfluencies that disrupt communication, while in others, it appears mildly and has little impact on their ability to communicate. Moreover, stuttering severity is not constant within individuals; it can fluctuate in different time periods and situations depending on various factors such as the presence of an audience, affective state, communicative intent, and time pressure (Bauerly et al., 2019; Jackson et al., 2016, 2021; Jon & Esther, 1945; Sheehan et al., 1967). For example, PWS do not stutter when they speak out loud to themselves (so called “private speech”; Jackson et al., 2021) or some PWS can eliminate stuttering when speaking alone (for a more detailed discussion, see the chapters 5 and 6 of this thesis), but stuttering emerges when they aim to convey information to another agent. This heterogeneity makes it challenging to pinpoint a stable neural signature. Moreover, this inconsistency complicates efforts to measure stuttering severity reliably, as traditional assessment methods, which typically rely on brief observational samples, may not capture the full range of the severity.

To provide a comprehensive account of stuttering, I will build my arguments based upon the "demands and capacities" framework, which proposes that stuttering occurs when the vulnerable speech motor system is overloaded by the cognitive and social demands of communication (Adams, 1990; Smith & Weber, 2017). In this context, I will review neurobiological theories and evidence under the concept of "capacities," reflecting the differences in the speech motor control of PWS. Specifically, I will put forward three dominant theoretical frameworks "disrupted auditory prediction account" (Civier et al., 2010; Max et al., 2004; Max & Daliri, 2019) and "the impaired left hemisphere basal ganglia motor loop account" (Alm, 2004; Chang & Guenther, 2020; Civier et al., 2013). Another dominant neurobiological theory of stuttering, "the incomplete cerebral dominance theory" will be elaborated in detail under chapter 3. Psychological factors will be examined under the "demands" section, which will be further categorised into psychological and linguistic demands. In the general discussion of the thesis, I will synthesise our findings with existing theories to propose an unified model that accounts for within and between individual variability and to explain fluency-enhancing conditions, aiming to provide a nuanced understanding of the stuttering phenomenon.

## 1.3.1 Capacities

### 1.3.1.1 Structural differences

Unlike conditions such as a stroke, where brain scans can reveal clear areas of damage, or epilepsy, where abnormal electrical activity is clearly evident in EEG recordings, stuttering does not present with obvious pathophysiological changes on clinical imaging (Neef & Chang, 2024). Nevertheless, structural studies employing diffusion tensor imaging (DTI) provided compelling evidence that stuttering is associated with atypical white matter characteristics, especially underlying white matter of the left hemisphere's pre-motor and primary motor speech-related areas involved in articulation and sensorimotor integration (Chang et al., 2008; Cykowski et al., 2010; Kell et al., 2009; Sommer et al., 2002; see Neef et al., 2015 for a review). Other studies replicated the previous findings and reported more extended differences in structural connectivity within the posterior body of the corpus callosum, basal ganglia, corticospinal tracts, and

cerebellum, which are important for selecting, coordinating and initiating precise motor movements (Connally et al., 2014; Watkins et al., 2008a). In support of these findings, a longitudinal study of 95 children who stutter and 95 fluent controls found that spontaneous recovery was associated with age-related growth in white matter volume, including the corticospinal tract, superior longitudinal fasciculus, arcuate fasciculus, somatomotor regions of the corpus callosum, and cerebellar peduncles (Chow et al., 2023).

Neurogenic stuttering has been typically linked to damage in the left hemisphere's speech-related areas, particularly the left striatum (Theys et al., 2013). In a more recent study, lesions that result in acquired neurogenic stuttering have been mapped to a consistent network in the brain, centered around the left ventral putamen, claustrum, and the amygdalostriatal transition area (Theys et al., 2024). Left putamen involvement is vital as the putamen receives input from motor-related cortical areas like M1, premotor cortex, and SMA, and processes these signals to relay them back via basal ganglia and thalamus to the SMA. As discussed previously, this circuit is involved in coordinating the timing, selection, and sequencing of speech movements, and interruptions within it can disrupt fluency. In a further analysis from the same group reported that higher grey matter volume in this lesion-based network correlates with symptom severity in developmental stuttering, as measured by the Overall Assessment of the Speaker's Experience of Stuttering (OASES) (Theys et al., 2024).

Further evidence in structural differences comes from a replication analysis which reported significant fractional anisotropy reductions in the left hemisphere of PWS, particularly in late-myelinating fibers, linked to elevated radial diffusivity, suggesting potential abnormal myelogenesis in these areas, therefore reduced speed of communication (Cykowski et al., 2010). On a related note, axonal stimulation of frontal aslant tract, a white matter pathway connecting the inferior frontal gyrus to SMA and thought to be important for coordinating speech initiation, has been shown to induce temporary stuttering (Kemerdere et al., 2016). Furthermore, quantitative mapping imaging revealed elevated iron content in putamen (Cler et al., 2021), likely resulting from dopaminergic irregularities or lysosomal disfunction, a circumstance in which

lysosomes fail to effectively break down waste materials within cells. It is worth noting that, Wu and colleagues (Wu et al., 1997) reported elevated levels of dopamine in striatum, however this study was conducted with a small sample size of three PWS.

The structural differences in the areas associated with the left hemisphere basal ganglia motor network have been interpreted by many scientists (Alm, 2004; Civier et al., 2013; Chang & Guenther, 2020) such that this excess dopamine might disrupt the inhibition required to suppress competing motor programs, making it difficult to select the correct speech motor commands. Supporting this idea, medications like haloperidol and risperidone, which block dopamine D2 receptors in striatum (thereby enhancing the inhibitory control of the indirect pathway to suppress unwanted motor commands), have been shown to reduce stuttering symptoms (Burns et al., 1978; Maguire et al., 2010; Maguire et al., 2004). On the other hand, insufficient dopamine can also disrupt motor command selection by weakening the transmission of signals for the appropriate motor program (Tecuapetla et al., 2016). This underscores the dynamic nature of dopamine signalling, which follows an inverted U-shaped curve for optimal balance, varying with specific situations and learned experiences, and suggests that disruptions in the equilibrium between the direct and indirect pathways of the basal ganglia may contribute to the fluctuating severity of stuttering in different contexts (Alm, 2021).

#### 1.3.1.2 Capacity of the sensorimotor integration system

The neural correlates of stuttering are explored in depth in chapters 2 and 3 of this thesis. Here, I will outline some of the key findings that have informed these studies. Multiple meta-analysis from brain imaging studies have reported functional differences in regions involved in both feedforward and feedback control of speech (Belyk et al., 2017; Brown et al., 2005; Budde et al., 2014). A recent meta-analysis revealed a correlation between stuttering and decreased activity in the left laryngeal motor cortex, that encodes the articulation of speech sounds (Belyk et al., 2017). Both fMRI and electrophysiological studies have revealed atypical activation patterns in the auditory cortex of PWS, with neuroimaging (PET and fMRI) showing diminished or absent activation in this region (Brown et al., 2005), whereas electrophysiological research has identified

altered auditory modulation prior to speech onset (Daliri & Max, 2015b; Max & Daliri, 2019). These findings imply that PWS may struggle with integrating sensory feedback into their speech motor control, potentially due to deficiencies in evaluating efference copies. Supporting this view, an elegantly designed EEG study reported differences even when PWS were passively listening to their own pre-recorded speech, without any articulation (Daliri & Max, 2015a). The authors interpreted these results by arguing that the issue lies not in generating motor commands but in using forward models to predict the sensory consequences of those commands.

Some fluency-enhancing conditions such as choral speech (speaking in unison with another voice), delayed auditory feedback (DAF), frequency-altered feedback (FAF), and masking noise can temporarily improve speech fluency (Adams & Hutchinson, 1974; Altrows & Bryden, 1977; Kalinowski & Saltuklaroglu, 2003; Peter Howell, 2004; Saltuklaroglu et al., 2009). These methods are thought to bypass the disruptions in sensorimotor integration, providing support to the idea that stuttering is linked to difficulties in integrating sensory and motor processes. A detailed exploration of temporary fluency-enhancing techniques that target sensorimotor integration is presented in chapter 5.

In the unstable internal models hypothesis, Max and colleagues (2004) proposed that stuttering in some children may derive from difficulties in forming stable and accurate mappings between motor commands and their sensory consequences. These mappings are essential for fluent speech and come in two shapes: inverse and forward mappings (note that these terms are different to the feedforward and feedback controller systems mentioned previously). Inverse mappings involve determining which motor commands are needed to achieve a specific sensory goal, such as knowing how to position the tongue and lips to produce the sound “c”. Forward mappings, on the other hand, allow the brain to predict the sensory feedback that will result from a given motor command, such as predicting how saying the word “Charlie” should sound, before actually articulating it. The feedforward controller relies on these established mappings to carry out articulatory movements without needing real-time sensory feedback. If the mappings are not updated or activated accurately, the feedforward system cannot predict and initiate motor

commands effectively. Problems in updating internal mappings would especially be challenging during childhood, as rapid changes in brain development and the structure of the vocal tract require the brain to continually adjust its internal models, to keep up with these physical changes (Vorperian et al., 2009). Overall, Max and colleagues (2004) suggested that in stuttering, the brain may struggle to update or effectively activate internal models, potentially due to structural differences found in stuttering.

While Max and colleagues (2004) proposed that PWS could benefit from relying more on sensory feedback to compensate for difficulties in the feedforward controller, Civier and colleagues (2010) argued that stuttering may result from an overreliance on auditory feedback, as it is not fast enough to facilitate articulation. To test their argument, they used a modified version of the DIVA model to simulate stuttering (Civier et al., 2010). They demonstrated that producing a word like “bid” generates more errors than “bad” because the vowel “i” necessitates a quicker transition than “a”. Since the feedback controller operates more slowly phonemes requiring rapid transitions, particularly those involving the tongue moving from a posterior to an anterior position or vice versa (F2 values), are prone to errors. These accumulated errors can lead to repetitions, as the monitoring system detects significant mismatch between the efference copy and auditory feedback and, restarts the syllable repeatedly until the error is minimised. Speaking at a slower pace reduces these production errors and, consequently, the occurrence of stuttering (Andrews et al., 1982; Ingham et al., 1974). This hypothesis is supported by recent findings using real-time fMRI, which have shown considerable variability in tongue movements even during the fluent articulation of pseudowords (Wiltshire et al., 2021). Furthermore, most repetitions tend to occur at the beginning of syllables initiated by consonants (Bloodstein, 2021; Civier et al., 2010), which suggests that these speech elements requiring rapid formant transitions, are particularly susceptible to auditory feedback errors. For instance, the stuttering DIVA model shows the largest auditory errors on initial phonemes of words (Civier et al., 2010). However, this explanation may not account for silent block symptom of stuttering, which occurs even before articulation begins. Therefore, stuttering can manifest in the absence of any production error. Stuttering can also

happen during the utterance of a single vowel without the need for a rapid F2 transition. For example, a person who stutters can experience a block while attempting to speak out a single vowel “e” when spelling out a name of a restaurant one letter a time, if there is a high information value on that vowel.

In conclusion, there is strong evidence that disruptions in sensorimotor integration influence fluent speech. However, further research is warranted to fully understand the temporal and spatial dynamics between the disruptions in the sensorimotor functions and initiation circuit, both playing an important role in neural correlates of stuttering.

#### 1.3.1.3 Capacity of the initiation circuit

Chang & Guenther (2020) and Civier and colleagues (2013) argued that the three core symptoms of stuttering (repetitions, prolongations, and blocks) derive from disruptions in the cortico-basal ganglia-thalamo-cortical loop, which interfere with the initiation circuit of the feedforward controller. According to their model, a repetition occurs when the initiation signal for producing a phoneme temporarily falters, causing speech to begin but halt prematurely, and then restart. In the case of a prolongation, the inability to correctly find the context for ending the current phoneme results in extended production, as SMA does not deactivate the initiation signal at the proper moment. For blocks, the issue lies in the inability to detect the appropriate context for start the next phoneme, leading to a delay or failure in initiating speech, as the neurons in SMA for the following sound are not activated on time. It could be argued that disruptions in sensorimotor integration within the feedforward controller, may impair the striatum’s ability to detect the appropriate sensorimotor context for initiating speech.

Electrophysiological studies are valuable for investigating the temporal dynamics of the initiation circuit due to their high temporal resolution. Stemming from the electrophysiological results, the “communication through coherence” hypothesis (Fries, 2005, 2015; Weinrich et al., 2017) proposes that synchrony in neural oscillations supports effective communication between different brain regions. Neural oscillations are categorised by their characteristic frequencies, and

among these, beta oscillations (13-30 Hz) are especially significant in the motor system. Particularly, modulation of beta activity facilitates the initiation and termination of movement sequences (Bartolo & Merchant, 2015), with event-related desynchronisation (ERD) describing a reduction in beta power that occurs as the motor system prepares for movement and continues through its execution, and event-related synchronisation (ERS) reflecting an increase in beta power that stabilises motor activity post-movement. In basal ganglia, beta oscillations help integrate sensory cues to guide behaviour (Leventhal et al., 2012).

Research has shown that PWS show different speech-related neural dynamics across beta and other frequency bands in both children (Joos et al., 2014; Özge et al., 2004), and adults who stutter (AWS) (Etchell et al., 2016; Kikuchi et al., 2017; Mersov et al., 2016; Mock et al., 2016; Orpella et al., 2024; Saltuklaroglu et al., 2017; Sengupta et al., 2016). In a study by Mersov and colleagues (2016), AWS and controls were asked to produce a series of words embedded in carrier phrases while their neural activity was recorded using magnetoencephalography (MEG) to investigate differences in speech-motor network oscillations during the preparation and execution phases of articulation. The results showed that AWS displayed exaggerated beta suppression during ERD and increased ERS in the motor cortex during articulation. They interpreted the results as showing that exaggerated motor preparation in AWS reflects reduced coordination in the speech-motor network, where heightened beta synchronisation suggests an overly inhibited motor system requiring stronger beta suppression before speech initiation. Another MEG study examining pre-speech oscillatory differences during stuttered utterances found that increased beta power in the right pre-SMA, a key node for motor inhibition, reflects a “freeze” response triggered by the anticipation of stuttering (Orpella et al., 2024). These findings of different neural oscillations provide evidence that there are disruptions in the initiation circuit of speech in PWS.

As noted above, Mersov and colleagues (2016) suggested that higher beta activity during ERS may result from overly inhibited M1. To test this argument, transcranial magnetic stimulation (TMS) can provide researchers with a method to measure cortical excitability and motor thresholds directly by using magnetic pulses to stimulate specific brain regions. For example,

Neef and colleagues (2015) used TMS to elicit motor-evoked potentials in the tongue during speech production and found that fluent speakers displayed greater left-hemisphere excitability, which was absent in PWS. Another TMS study investigating different levels of speech production found that AWS had lower motor-evoked potential amplitudes and reduced facilitation ratios in the tongue compared with controls, especially during immediate speech production conditions, indicating diminished motor facilitation before speech onset (Whillier et al., 2018). These findings were positively correlated with stuttering severity, suggesting an imbalance between excitatory and inhibitory cortical activity in PWS. Supporting these results, a meta-analysis of neuroimaging studies by Belyk et al. (2017) showed reduced activation in the left M1 laryngeal region during speech in PWS. This decreased neural activity in M1 may be linked to disfunction in the cortico-basal ganglia loop, which plays an important role in modulating inhibitory and facilitatory processes during speech planning and initiation (Civier et al., 2013; Neef et al., 2011; Chang & Guenther, 2020).

Perhaps the strongest evidence supporting the involvement of the initiation circuit in stuttering comes from the immediate elimination of stuttering with metronome-paced speech (Fransella & Beech, 1965; Howell & El-Yaniv, 1987). This temporary fluency-enhancing effect is thought to bypass unbalanced activity in the cortico-basal ganglia-thalamo-cortical network, responsible for selecting and initiating motor commands (Alm, 2004; Civier et al., 2013; Chang & Guenther, 2020). The rhythm of the metronome may offer an alternative motor pathway, shifting control from the impaired internal initiation circuit to external cues, which can also be observed in movement disorders like PD (Jahanshahi et al., 1995). In PD, dopamine depletion impairs basal ganglia function, and external cues such as rhythmic auditory signals or visual markers can significantly improve motor control, particularly enhancing gait patterns and movement coordination (Bagley et al., 1991; Glickstein & Stein, 1991).

Supporting the link between PD and stuttering, a study on neurogenic stuttering caused by missile wounds from the Vietnam War found that 7 out of 10 patients had lesions in putamen and pallidum, that are commonly affected in PD (Joutsa et al., 2018; Ludlow et al., 1987). Deep brain

stimulation of the globus pallidus in people with PD can trigger new instances of stuttering, supporting the involvement of the basal ganglia initiation circuits in stuttering (Rusz et al., 2018). This is further supported by findings that stimulation of the subthalamic nucleus can exacerbate stuttering in Parkinson's patients (Toft & Dietrichs, 2011) and that targeting the globus pallidus or thalamus to treat dystonia can have similar effects (Allert et al., 2010; A. Nebel et al., 2009). However, the opposite effects have also been observed, with deep brain stimulation of the subthalamic nucleus in PD, that relieved acquired stuttering (Walker et al., 2009). Thus, the paradoxical effects of deep brain stimulation, which can either induce or alleviate stuttering depending on the site of stimulation and individual, further strengthen the case that stuttering evolves from deficits in the initiation circuits of basal ganglia, with external pacing mechanisms potentially offering a compensatory route for fluent speech.

Singing is another phenomenon that eliminates stuttering, primarily because its rhythmic and melodic structure provides external timing cues that bypass the brain's internal initiation circuits. Although the motor control circuits for both speech and singing are similar, singing specifically engages the dorsal regions of the precentral gyrus (Zarate & Zatorre, 2008; Zuk & Guenther, 2022). Previous research showed that auditory rhythmic cues, such as those found in singing, strongly activate the dorsal premotor cortex during synchronisation to musical rhythm (Chen et al., 2006; Jäncke et al., 2000; Pollok et al., 2009). Additionally, skilled pianists exhibit stronger activation in the dorsal premotor cortex due to their auditory-motor training (Baumann et al., 2007), and macaques trained to reproduce pitch sequences activate these regions when listening to learned sequences (Archakov et al., 2020). This reliance on rhythmic timing and pitch control in singing engages the dorsal route of precentral gyrus more strongly, bypassing the ventral route and internal initiation circuits required for speech and possibly resulting in fluent vocalisations in PWS.

#### 1.3.1.4 Therapeutic approaches to increase capacity

Achieving persistent and natural speech fluency in PWS continues to be an ongoing challenge. While fluency-shaping techniques that modify speech through behavioural training have shown

some improvement, such as by slowing speech, employing gentle articulatory onsets, and managing breath control (Brignell et al., 2020; Ingham & Andrews, 1973; R. L. Webster, 1980), these methods interfere with the natural flow of speech and are linked to high relapse rates (Tasko et al., 2007). Effectively engaging neuroplasticity mechanisms to improve speech fluency without altering the natural quality of speech in social situations may offer a more promising approach. Neuroplasticity allows the brain to strengthen weak neural circuits that support more automatic and effortless speech motor control after the training, which can avoid the socially and cognitively demanding fluency shaping techniques. In stroke recovery, for instance, repetitive task-specific exercises help the brain restore lost motor functions, including speech, through neuroplastic changes (Krakauer et al., 2012).

Following this line of research, Toyomura and colleagues (2015) reported that 8 weeks of metronome-paced speech practice, which targeted the initiation circuit, led to normalised basal ganglia activity compared with controls during a speech task in fMRI along with improvements in self-paced speech fluency. In a similar vein, another study targeted neuroplasticity in both the initiation and sensorimotor circuits through speech training during metronome-paced and choral speech separately, but with the added element of transcranial direct current stimulation (tDCS) applied over the left inferior frontal cortex (Chesters et al., 2018). They reported similar findings to Toyomura and colleagues (2015), showing normalised brain activity in the cortico-basal ganglia-thalamo-cortical loop (Chesters et al., 2021) and improved speech fluency (Chesters et al., 2018). However, the use of brain stimulation appeared to accelerate neuroplastic changes, reducing the required time for these improvements from eight weeks to just one week. It is worth to note that while fluency improvements were maintained during reading, the enhanced fluency did not generalise fully to conversational speech after 6-weeks (Chesters et al., 2018), highlighting the need to address both capacity and demand aspects of stuttering in future interventions. Further research focused on the sensorimotor integration circuit by applying anodal tDCS over the left superior temporal gyrus with DAF, which significantly reduced stuttering severity and improved fluency for up to six weeks after the intervention (Moein et al., 2022). These results show the

potential of neuromodulation to enhance the long-term effects of fluency treatments either by targeting the sensorimotor integration or initiation circuits or both.

There is currently no globally approved pharmacological treatment for stuttering. Research continues to explore several pharmacological interventions with many focusing on modulating dopamine due to its role in the initiation circuit (Maguire et al., 2020). For example, one study investigated the effects of risperidone, a dopamine D2 and serotonin 5-HT2 receptor antagonist, on brain metabolism in AWS (Maguire et al., 2021). In this randomised, double-blind, placebo-controlled trial, participants were treated with risperidone for six weeks, and PET scans revealed increased glucose uptake in the left striatum and left inferior frontal gyrus, highlighting the potential of pharmacological treatments, especially if combined with speech therapy in the future. On the other hand, serotonergic agents like paroxetine, which decrease serotonin reuptake, have shown no benefits in alleviating stuttering symptoms (Stager et al., 2005). GABAergic compounds, such as pagoclone, a partial GABA-A agonist, have also been tested with mixed results, as a trial of pagoclone did not show significant reductions in stuttering (Maguire et al., 2010). It is worth noting that, while some of these pharmacological approaches show promise, their overall effectiveness stays inconsistent and warrants further investigation.

### 1.3.2 Demands

To see the full picture of stuttering, we must also consider the aspect of demands placed on the speaker. The fluency-enhancing effect of singing or choral speech are already fascinating on their own, but perhaps it is the demand factors that makes stuttering such an enigmatic condition: PWS can speak to themselves fluently when there is no audience present without changing their natural quality of their voice or adapting any fluency shaping techniques (Jackson et al., 2021). It also needs to be acknowledged that investigating the neural correlates of some of these demands presents considerable challenges for researchers. For instance, it is reported that PWS do not stutter when they direct their speech to themselves (Jackson et al., 2021). However, convincing someone to be completely alone and speaking to themselves without any communicative intent in a neuroimaging setting, such as an MEG or fMRI scanner, is difficult because even the

perception of being observed can trigger stuttering (Hahn, 1940; see Chapter 5 for our results). Portable tools like Functional Near Infrared Spectroscopy may offer the possibility of recording brain activity in a more natural home setting, but even knowing their brain activity is being monitored can affect fluency. With these challenges in mind, in this section, I will explore the factors that modulate stuttering according to the current literature, dividing them into two categories: psychological and linguistic demands.

#### 1.3.2.1 Psychological demands

One of the most prominent features of stuttering is its variability, not only across different social situations but also from moment to moment (Constantino et al., 2016; Tichenor & Yaruss, 2021). Alm (2014) proposed that this variability might be driven by the interference of "social cognition", where a speaker's perceptions of themselves or mentalising with the audience's expectations put additional demands on an already fragile speech-motor system. The evidence that PWS do not stutter when talking to themselves alone without any communicative intent (Jackson et al., 2021) supports the idea that stuttering is not solely a motor issue but is heavily influenced by psychological factors such as the presence of an audience and mentalising on audience's expectations, hesitancy of accurate and appropriate information transfer, negative self & social evaluation, physiological arousal and time pressure (Alm, 2014; Hahn, 1940; Jackson et al., 2016; Jon & Esther, 1945; Perkins William; Kent Raymond; Curlee Richard, 1991; Peters & Guitar, 1991; Quarrington, 1965; Sheehan et al., 1967; Smith & Weber, 2017).

Alm's (2014) proposal focuses on the interaction between the social cognitive network and the goal-directed network, which is instrumental in actions like speech formulation and involves regions such as M1, the SMA, and the ventral frontal cortex (Fox et al., 2005). In contrast, the social cognitive network, responsible for processes like social reasoning and audience perception, typically operates independently of motor control (Spreng et al., 2013). The hypothesis is that in PWS, the social cognitive network may interfere with the goal-directed network by generating "noise" that disrupts fluent speech (Alm, 2014; Jackson et al., 2016). This could explain why PWS speak more fluently when alone but experience disfluencies in social settings. It is worth

noting that, some PWS can eliminate stuttering when alone, even while imagining social encounters, feeling anxiety, recording their voice (see our results in chapter 5) or during mind-wandering, which activates the default mode network, and is thought to interfere with fluency (Alm, 2014, section 8.5; Smith and Weber, 2017). This suggests that implicit processes, rather than conscious feelings or attentional focus, may play a stronger modulatory role in causing stuttering.

Peters and Guitar (1991) described the psychological factors in stuttering as part of an implicit learning process, where stuttering can be understood as a type of "freeze" response that inhibits articulation. This inhibitory response may be selectively applied to speech motor functions, with the brain associating stuttering events as threats over time, based on negative self and social evaluation. For instance, a child experiencing whole-word repetition might initially display a benign disfluency. However, if the child receives negative reactions to these disfluent moments from family members or peers, whether through judgements about their intelligence, frustration, neglect or teasing, this can lead to the child's threat detection system associating every stuttering moment as a threat (Guitar, 2019).

Since this freeze response is a learned behaviour, it can explain both individual differences and variability within the same person over time. For instance, while PWS may speak fluently in non-communicative contexts, such as when talking to themselves (Jackson et al., 2021), disfluencies emerge when conditioned threats are present. Higher-order conditioning may extend this threat association to new communicative situations, such as recording one's voice, speaking to someone with higher social status, ordering food or saying words of high personal significance, like one's name or many other contexts. Each of these associations may carry different weight for different individuals or at different times, taking into consideration the moment-to-moment variability in stuttering and individual differences. The theory of learned freeze response is supported by research showing higher inhibitory activity and maladaptive processes in sensorimotor networks of speech, which correlate with both stuttering severity (Korzeczek et al., 2022; Neef et al., 2018) and stuttered moments (Orpella et al., 2024). Additionally, higher activity in threat-related brain

regions, such as the right amygdala (Šimić et al., 2021; Toyomura et al., 2018; Yang et al., 2017), further supports the role of threat conditioning in modulating stuttering, as discussed in detail in the final chapter.

In situations of heightened emotional arousal, such as rage, the brain may shift from the freeze response to a fight-or-flight state. This shift has been interpreted to facilitate fluent speech by overriding freezing, as the brain prioritises immediate, unfiltered action (Alm, 2004b). This idea is supported by historical reports, such as Bloodstein's (2021) account of two people who stuttered, yet were able to speak fluently only in life-threatening situations during World War II (Alm, 2004b). Furthermore, it is common knowledge among PWS, some people experience greater fluency during states of rage or heightened emotional arousal (e.g., Reddit.com, 2000), such as when urgently calling an ambulance for a loved one. In such scenarios, the path of action becomes clear, and the increased sense of control brought on by rage or heightened arousal state may override the inhibitory mechanisms tied to speech (Alm, 2004b).

Another line of empirical support for the role of psychological demands in stuttering comes from research on the correlation between the informational value of words and stuttering (Quarrington, 1965; Soderberg, 1971; Wingate, 1979; see Brundage & Bernstein Ratner, 2022 for a review). The information value of a word refers to the degree of meaning or importance it conveys within a specific context. Words with higher informational value, such as key nouns or names, play a critical role in the listener's understanding of the message (Kaasin & Bjerkan, 1982). In simple terms, words that are less predictable by the listener carry higher informational value (Wingate, 1979). While this concept could be considered a linguistic demand, it fits well under psychological demands as well because the speaker mentalising on the listener's knowledge and expectations, anticipates the communicative importance of certain words while striving to convey information accurately under time pressure. The fear of failing to do so may be linked to concerns about negative self or social evaluation, potentially triggering a threat response. For instance, in a sentence like, "The meeting starts at three ___", the word "o'clock" is highly predictable and carries low informational value, making it less likely to cause stuttering. However, in a sentence

such as, “My name is ___”, the word is less obviously predictable and carries higher informational weight, increasing the pressure to convey the information accurately using speech and, consequently, the likelihood of stuttering. This explains why uttering personal names or initiating sentences, which tend to have high informational value, commonly gives rise to disfluencies in PWS.

One of the psychological phenomena in stuttering is the conscious anticipation by PWS that they will stutter on certain words before they even begin speaking (Jackson et al., 2015, 2019; Wingate, 1975). This anticipation can arise both in the moments seconds before articulation or long in advance, such as when PWS imagine speaking a particular word, like their name during a job interview, weeks beforehand (Jackson et al., 2015). From a Bayesian perspective, this can be understood as a predictive coding model, where PWS generate internal predictions about the likelihood of stuttering based on past experiences, repeated stuttering on specific words strengthens these learned priors, making the brain expect stuttering on the same words. Orpella and colleagues (2024) suggested that the increase in self-monitoring and control during speech production, particularly before anticipated stuttered utterances compared with before a fluent one (Jackson et al., 2022) may be linked to an internally directed focus, which is known to disrupt automatic movements (Kal et al., 2013).

However, it is unclear whether conscious anticipation is a cause, a modulator, or simply a learned prediction of stuttering. Bayesian models emphasise the probabilistic nature of these predictions, meaning that while anticipation is associated with higher chances of stuttering, it may not cause it. For instance, PWS may expect to stutter on a certain word, but a stutter is not guaranteed (Jackson et al., 2022). Another example is that PWS may read fluently to themselves when alone, even if they anticipate stuttering on certain words. This suggests that conscious anticipation of stuttering and implicit threat conditioning may interact but are not the same phenomenon. This distinction is further supported by people with apparently mild or even no stuttering who report conscious anticipation of stuttering but do not overtly stutter, which is sometimes referred to as covert or interiorised stuttering. It is also worth noting that threat conditioning is a form of

associative learning, but it is non-declarative, which means it is implicit and does not always result in a conscious experience or feelings. Research has shown that physiological threat detection and threat response can occur without individuals being aware of it (Dolan & Vuilleumier, 2003; Phelps, 2006; see also LeDoux & Pine, 2016). Therefore, even though there may be interaction between the consciously learned predictions of stuttering, and the implicit threat conditioning, it is important to consider evaluating them separately.

As mentioned earlier, PWS are more likely to develop affective disorders such as social anxiety, fear of speaking, and shame, all of which significantly impact their quality of life (Blumgart et al., 2010; Craig & Tran, 2014; Iverach & Rapee, 2014; Peters & Starkweather, 1989; Iverach et al., 2009; Yaruss, 2010). These emotional responses, such as anxiety about negative social evaluation before speaking, increased self-monitoring during speech, and feelings of shame afterwards. I argue that these factors contribute to the deep entrenchment of implicit threat conditioning, with conscious feelings like anxiety and shame reinforcing the threat response as both processes interact over time. However, it is important to distinguish between conscious feelings and implicit threat conditioning, as they are not identical, mentioned above. Thereby, treatments that focus exclusively on addressing conscious feelings may be effective at reducing social anxiety and other feelings but are unlikely to directly improve speech fluency. Similarly, fluency-focused treatments may alleviate negative feelings if fluency is achieved naturally, but they are unlikely to fully address the deeply entrenched underlying emotional and psychological challenges PWS face. In the final chapter, I will propose a comprehensive treatment protocol that addresses all the pillars of both the capacity and demand aspects of stuttering, combining exposure therapy with innovative fluency treatments, including brain stimulation and virtual reality, to offer a more holistic approach.

#### 1.3.2.2 Linguistic demands

There is evidence that linguistic factors influence stuttering frequency (Karniol, 1995), with certain types of words and sounds being more likely to trigger disfluencies. Brown (1945) identified four key linguistic features that tend to increase stuttering in PWS: longer words,

content words (such as nouns, verbs, adjectives, and adverbs) rather than function words (like articles, prepositions, pronouns, and conjunctions) for adults, initial consonants, and words at the beginning of sentences. In contrast children who stutter (2 to 6 years), tend to exhibit disfluencies more frequently on function words (Peter et al., 1999). However, as they grow older, disfluencies decrease on function words and become more common on content words, as reported by Howell and colleagues (1999). Some studies showed that stuttering is more common at the start of sentences, especially when the planned utterance is long (Jayaram, 1984). Conversely, stuttering rarely occurs on single-word utterances or word lists. These findings suggest that the linguistic structure of speech interacts with the underlying mechanisms of stuttering, making certain linguistic elements more challenging for PWS (Guitar, 2019).

Previous research has shown that as the linguistic demands of speech increase, so does the variability in motor execution, particularly in PWS (Smith et al., 2010). For example, Smith and colleagues (2010) examined the effect of phonological complexity on articulation by recording lip movements in both PWS and fluent controls as participants repeated pseudowords of varying length and phonological complexity. Simple pseudowords, such as “mab”, were compared with more complex ones, such as “mabteebeebee” (longer) and “mabshaytiedoib” (phonologically more complex). The results showed that while both groups exhibited increased variability with greater linguistic complexity, this effect was significantly stronger in PWS.

Overall, stuttering cannot be understood solely based on neural differences, as PWS do not stutter during private speech (Jackson et al., 2021). As reviewed, there is compelling evidence that stuttering is influenced by various demands placed on the speaker, including psychological and linguistic factors. Psychological demands, such as the presence of an audience, communicative intent, and the informational value of articulation, impact fluency. The learned freeze response, linked to threat conditioning, may be triggered by perceived threats based on past negative experiences and likely acts as a modulator affecting the neural correlates of stuttering (Peters & Guitar, 1991). Linguistic demands also influence stuttering, with specific word characteristics and sentence structures contributing to disfluency rates. As linguistic complexity increases, PWS

experience greater variability in articulation, which suggests an interaction between linguistic and speech motor control in stuttering.

## 1.4. Thesis outline and objectives

The primary goal of this thesis is to contribute to the understanding of the neural correlates of stuttering and to explore practical interventions that could assist PWS who wish to work on their fluency. To achieve this, the thesis comprises four studies. My first two fMRI studies are distinguished by their relatively large sample sizes in neuroimaging. My third study used a novel non-invasive brain stimulation protocol to improve sensorimotor learning in speech. And my final study includes a creative approach that I developed to eliminate stuttering during presentations.

The first study investigates the neural correlates of developmental stuttering using a pooled dataset of four different fMRI studies. By analysing data from 56 PWS and 53 typically fluent controls, the study investigates the differences in brain activity between the groups during a sentence reading task. The second fMRI study revisits the incomplete cerebral dominance theory, which suggests altered language lateralisation in PWS. I conducted a threshold-independent laterality analysis to statistically compare the functions of both hemispheres derived from four different speech and language tasks.

In the third study, the focus shifts to test a novel brain stimulation technique aimed at enhancing sensorimotor learning in speech. This study employed theta-gamma phase-amplitude coupled transcranial alternating current stimulation to investigate its impact on speech to altered auditory feedback in 60 typically fluent speakers. The final study explores a practical approach to eliminate stuttering during presentations by utilising the fluency-enhancing effect of choral speech in a creative approach.

Overall, with this thesis, I aim to contribute to our understanding of the neural and psychological correlates of stuttering and to develop innovative methods for fluency enhancement. In the general discussion, I present a unified theory of stuttering, developed from the findings and literature review, that integrates evidence into both neural and psychological correlates. I conclude the

thesis with a proposal for future research by introducing the BraveVoice Stuttering Treatment Protocol, which aims to achieve fluent speech in spontaneous communication in real-life without compromising speech naturalness while also reducing social anxiety.

# 2

# Differences in brain activity during sentence repetition in people who stutter: a combined analysis of four fMRI studies


## Abstract

Our understanding of the neural correlates of developmental stuttering benefits from the use of functional MRI (fMRI) during speech production. Despite two decades of research, however, we have reached little consensus as to the anatomical basis of stuttering. In the current study, we pooled data from four fMRI studies that used the same methodological approach and task of sentence reading, allowing us to investigate brain activity with a relatively large sample. We analysed data from four different studies for 56 adolescents and adults who stutter and 53 demographically-matched typically fluent controls while performing an overt sentence reading task. A sparse sampling design was used in all the studies, in which participants spoke during the silent period between measurements of brain activity. We did not exclude any stuttering epochs from the data. Sentence reading evoked activity in both groups across frontal and temporal regions bilaterally. In the group comparison, people who stutter (PWS) showed greater activity ($Z > 2.3$, $k > 30$ voxels, uncorrected) compared with controls in the right anterior frontal cortex, right anterior insula extending to the frontal operculum, left planum temporale, and midbrain, at the level of the red nucleus. In contrast, PWS showed lower activation in left superior frontal sulcus, subgenual medial frontal cortex, right anterior temporal lobe and portions of the inferior parietal lobe bilaterally including the angular gyrus on the left. Even with this relatively large sample size, group differences in task-evoked activity did not pass the statistical threshold for spatial extent when a cluster-forming threshold of $Z > 3.1$ was used. However, at a lower uncorrected voxel-wise threshold, we observed some results consistent with earlier meta-analyses of functional imaging studies in stuttering; for example, overactivity in the right anterior insular cortex.

Surprisingly, even with this low threshold ($Z > 2.3$), we did not find any support for findings related to cerebellum or M1 previously reported in meta-analyses. In sum, even by pooling data across several small studies to achieve a reasonable sample size, we have found only statistically-weak functional differences between groups in cortical and subcortical regions associated with speech-motor control.

## 2.1 Introduction

Stuttering is a complicated neurodevelopmental disorder that affects about 1% of the adult population worldwide. It is characterised by disruptions in the flow of speech, with symptoms typically appearing in early childhood, usually between the ages of two and four (Yairi & Ambrose, 2013). The aetiology of stuttering involves a complex interplay between neurobiological and environmental factors. Recent neuroimaging studies have significantly improved our understanding of the brain regions involved in stuttering, showing both structural and functional differences in areas responsible for speech motor skills, sensorimotor integration, error monitoring, cognitive functions, and emotional regulation (for a comprehensive review: (Neef & Chang, 2024). However, there is still no definitive consensus on the core neural correlates of the disorder.

Meta-analytical approaches of fMRI and positron emission tomography (PET) data have improved our understanding of functional differences between PWS and typically fluent speakers. By combining results from multiple studies, three different meta-analyses have attempted to identify the neural substrates of stuttering during speech tasks (Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014). The first meta-analysis, encompassing eight PET and fMRI scans, revealed three key 'neural signatures' of stuttering: overactivation of the right anterior insula/frontal operculum, underactivation of the auditory cortex, and overactivation of the cerebellar vermis (Brown et al., 2005). Reduced activity in the auditory cortex is thought to act as a compensatory mechanism to reduce error detection due to disrupted sensorimotor integration through its connections with the striatum; this disruption means that when auditory feedback from speech does not match the efference copy of the intended motor command, it has been thought that the striatum detects this inconsistency, resulting in difficulties in initiating speech motor programs and consequently causing stuttering (Max et al., 2004). The observed differences in cerebellar structures between PWS and fluent individuals (e.g., Connally et al., 2014; Yang et al., 2016) have been interpreted that the cerebellum compensates for stuttering by assisting in the coordination and timing of speech motor actions to mitigate fluency disruptions (Kell et al., 2018);

for instance, fluency training has been shown to increase cerebellar activity associated with learning new speech patterns (De Nil et al., 2001).

Following these initial findings, subsequent meta-analyses have yielded varying results on the neural underpinnings of stuttering. One meta-analysis failed to replicate the cerebellar vermis finding but confirmed increased activation in the right insula and decreased activation in the left temporal lobe in PWS (Budde et al., 2014). It also reported novel findings of increased activity in supplementary motor area (SMA), which is important for initiating motor movements, and decreased activity in the left red nucleus. Belyk and colleagues conducted a similar meta-analysis in 2015, and corrected it afterwards for implementation errors that previously affected statistical thresholds due to a software glitch. Their updated analysis retained few robust effects from earlier studies, failing to replicate previous cerebellum and temporal lobe findings but identifying increased activity in the right Rolandic operculum and decreased activity in the left orofacial pre/primary motor cortex, which are key brain regions for articulation (Belyk et al., 2017).

Another critical structures implicated in stuttering are the basal ganglia, which play an important role in the selection, initiation, and termination of motor commands while inhibiting competing ones (Alm, 2004; Craig-McQuaide et al., 2014, Chang & Guenther, 2020). This connection between stuttering and basal ganglia emerged after an early imaging study identified elevated dopamine levels in the striatum of three PWS compared with six typically fluent controls (Wu et al., 1997). Furthermore, an fMRI study reported increased activity in a large subcortical area at the top of the brainstem encompassing several structures, including substantia nigra, pedunculopontine nucleus, red nucleus, and subthalamic nucleus (Watkins et al., 2008), suggesting functional differences at the subcortical level not captured by meta-analyses. Recent lesion network analysis reveals that neurogenic stuttering and persistent developmental stuttering share a common neural network, particularly in the left-sided posteroventral putamen, which controls the automation and internal timing of motor movements of articulators (Theys et al., 2024). Additional evidence for the causal role of basal ganglia motor circuits in stuttering comes from findings that deep brain stimulation over the globus pallidus internus (GPi) in Parkinson's

patients can induce stuttering (Nebel et al., 2009; Rusz et al., 2018). Levodopa treatment, which increases dopamine levels, can also exacerbate stuttering (Louis et al., 2001; Tykalová et al., 2015) by disrupting the inhibition of competing motor programs, highlighting that excessive dopamine may lead to insufficient inhibition to suppress competing motor programs, thus making it difficult to select the correct motor program over incorrect alternatives (Chang & Guenther, 2020).

Overall, these findings suggest that the neural circuitry in PWS may reflect either compensatory adjustments or inherent developmental differences. However, a clear consensus has not yet been reached in functional studies. This variability may arise from differences in experimental tasks (e.g., sentence reading, picture description), imaging modalities (e.g., PET, fMRI), methodological approaches (e.g., sparse vs. continuous sampling), and the use of fluency enhancement techniques (e.g., metronome pacing, choral speech). To address these discrepancies, we conducted a combined analysis of four fMRI studies using the same speech task and methodological approach, collected over time by the same research group. This approach lowers the confounding effects of individual study design differences and leverages a larger dataset to enhance the statistical power of our findings.

We pooled four different studies, three of which have been published (Watkins et al., 2008; Connally et al., 2018; Chesters et al., 2021, preprint) (see table 2.1 for scan details). In the study of Watkins and colleagues (2008), they showed overactivity in subcortical regions such as the midbrain, consistent with basal ganglia disfunction (mentioned above), and underactivity in cortical motor and premotor areas associated with articulation and speech production. Connally and colleagues (2018) focused on investigating state (e.g., disfluent speech moments) and trait effects (e.g., persistent differences in neural activity) in stuttering using fMRI. Their findings identified reduced activation in auditory and motor regions as general traits of stuttering, while disfluent states showed greater activation in bilateral inferior frontal and premotor areas, extending into the frontal operculum. Lastly, Chesters and colleagues (2021, preprint) investigated neural changes associated with a five-day intervention combining anodal transcranial

direct current stimulation over the left inferior frontal cortex with fluency-enhancing techniques. At the pre-intervention baseline, PWS showed lower activity compared with controls in several regions, including the right subcentral gyrus, medial parietal cortex extending to the paracentral lobule, and portions of the anterior cerebellum; while there were no regions where PWS showed higher activity than controls at baseline. Therefore, based on previous meta-analyses and the individual studies we pooled, we hypothesised that PWS would show differences in neural activation compared with controls. Specifically, we anticipated overactivity in regions such as the right anterior insular cortex, and the cerebellar vermis, alongside underactivity in the auditory cortex, and motor and premotor regions.

## 2.2 Methods

### 2.2.1 Participants

fMRI data were collected from four different cohorts over the past decade, comprising both adolescents and adults diagnosed with stuttering and matched control groups who were typically fluent speakers. The data were gathered during overt sentence reading tasks (see Demirel et al., 2024 for language laterality analysis of the same dataset). After applying exclusion criteria for excessive movement during scanning (detailed below), 5 PWS were excluded from the analysis and datasets from 56 PWS (10 females, 46 males; 7 left-handed; mean age = 28 years; age range = 14-54 years) and 53 control participants (13 females, 40 males; 2 left-handed; mean age = 28 years; age range = 14-53 years) were deemed suitable for analysis. Chi-squared tests indicated no significant differences between the groups in terms of handedness distribution (chi-squared = 2.73, p = 0.10) or gender distribution (chi-squared = 0.73, p = 0.39). Within the PWS group, stuttering severity, as measured by the Stuttering Severity Instrument (SSI) (Riley, 1994), ranged from very mild to very severe (range 9–46, median 26). The classifications of stuttering severity among the PWS group were as follows: very mild (n = 7), mild (n = 10), moderate (n = 23), severe (n = 11), and very severe (n = 5).

### 2.2.2 Speech task

The current analysis focused on the sentence reading task, as it constituted the largest dataset we could assemble from the four individual studies. Sentences were displayed in white font against a black background. In one study (16 PWS, 18 CON), a scene relevant to the sentence was also presented concurrently. Participants were required to read the sentences aloud and were able to listen to their own voice through headphones during the quiet intervals between scanning measurements. Baseline conditions were established through three different stimuli: a series of letter X's substituting for all characters in a sentence (17 PWS, 20 CON), sentences composed in the Farsi alphabet, which were not decipherable by the participants (23 PWS, 15 CON), and a fixation cross (16 PWS, 18 CON). These baseline conditions created a contrast between the mere perception of symbols with the articulation of meaningful sentences, allowing us to identify neural activity relevant to visual word recognition, semantic and syntactic processing, phonological assembly, articulation, and monitoring of self-produced speech.

### 2.2.3 FMRI data analysis

| Study | Baseline | PWS | CON | Scanner | TE (ms) | TR/TA (s) | Slices (N) | Thick-ness (mm) | In-plane (mm) |
|---|---|---|---|---|---|---|---|---|---|
| Watkins et al., 2008 | Row Xs | 10 | 10 | 3T Varian-Siemens | 30 | 10 / 3 | 32 | 4 | 4 x 4 |
| Unpublis hed data | Row Xs | 7 | 10 | 3T Siemens Trio | 30 | 10 / 3 | 50 | 3 | 3 x 3 |
| Chesters et al., 2021 (preprint) | Farsi script | 23 | 15 | 3T Siemens Trio | 30 | 9 / 2 | 38 | 3.5 | 3 x 3 |
| Connally et al., 2018 | Fixation | 16 | 18 | 3T Siemens Trio | 30 | 9 / 2 | 32 | 4 | 3 x 3 |

***Table 2.1: fMRI acquisition details.*** *The table summarises the scanning parameters used in the four studies included in the analysis. TE = Echo time (ms); TR = Repetition time (s); TA = Acquisition time (s); acquisition is delayed in sparse sampling designs to allow a silent interval between acquisitions resulting in a longer TR (= delay + TA); PWS: People who stutter; CON: Controls.*

FMRI data were analysed at the single-subject and group levels utilising the FEAT (fMRI Expert Analysis Tool) from the FMRIB Software Library (FSL; Woolrich et al., 2001). Echo-planar imaging (EPI) sequences went through several pre-processing steps to ensure comparability

across subjects. Initially, EPIs were corrected for head motion using FSL's MCFLIRT tool (Jenkinson et al., 2002), and spatial smoothing was applied using a Gaussian kernel with an 8-mm full-width at half-maximum. A high-pass filter with a cut-off of 90 seconds was applied to remove low-frequency noise while preserving task-related signals. Where applicable, field map-based distortion correction was performed to correct for magnetic field inhomogeneities. Subsequently, each subject's functional images were co-registered to their individual high-resolution T1-weighted structural images via boundary-based registration.

For further standardisation across the study cohort, these individual anatomical images were then registered to the standard MNI-152 brain template using the non-linear registration algorithm FNIRT, which is also part of FSL. To account for residual effects of head motion, six parameters obtained during the motion correction phase were included in the subsequent analyses as covariates of no interest.

The study employed a sparse temporal sampling technique (Hall et al., 1999) to minimise scanner noise interference during speech production. Sparse-sampling acquisitions have been shown to outperform continuous imaging in capturing auditory responses in the temporal lobe (Blackman & Hall, 2011; Gaab et al., 2007). Therefore, participants were instructed to speak only during silent intervals between scan acquisitions. This design allowed us to capture the haemodynamic response peak, which occurs 4-6 seconds post speech events.

Exclusion criteria were defined such that any dataset displaying an absolute mean head displacement of greater than 4 mm (exceeding the largest voxel dimension), or scans flagged by MCFLIRT for excessive motion during the session were excluded. Following these criteria, scans from five participants within the PWS group were omitted from further analysis; no datasets obtained in controls were excluded.

### 2.2.4 Statistical analysis

Task-related blood-oxygen-level-dependent (BOLD) activations were quantified using the general linear model in FSL's FEAT. For each participant, contrasts of interest were defined to compare the mean BOLD signal during overt sentence reading against the baseline rest condition. We used FMRIB's Local Analysis of Mixed Effects stage 1 (Woolrich et al., 2004) for the group-level analyses. These analysis was subsequently conducted using a cluster-forming threshold of $Z > 3.1$ and an extent threshold of $p < 0.05$, with family-wise error correction for multiple comparisons. We investigated the main effect of the task (sentence reading) between groups (PWS and CON). Main effect of group was examined using unpaired two-group comparisons with average speech activity relative to baseline and separate estimates of variance for each group.

When no significant differences in activity between groups were observed at this corrected threshold, we employed an exploratory approach using an uncorrected threshold of $p < 0.05$ ($Z > 2.3$), with the condition that clusters must include at least 30 voxels ($k > 30$). To maximise power, we included all speaking trials in this analysis. Had we found robust group differences, we planned to explore how these changed once stuttered epochs were excluded. Given the lack of differences, however, this planned analysis was not done (see discussion section for a more detailed discussion).

## 2.3 Results

### 2.3.1 Group averages

First, we analysed the BOLD activity for each group in comparison to the baseline conditions to identify group averages. Group-level statistical analyses were performed using a cluster-forming threshold of $Z > 3.1$, with cluster extent significance determined at $p < 0.05$, after correction for family wise error. Results indicated a broad activation within brain regions typically associated with speech and language production similarly in both groups (Fig. 2.1). Specifically, extensive bilateral activation was observed in the sensorimotor cortex, premotor cortex, and pre-supplementary motor area, extending to the anterior cingulate cortex. Additional significant

activity was noted in the superior temporal lobe, thalamus, ventral occipito-temporal cortex, and lobule VI of the cerebellum.

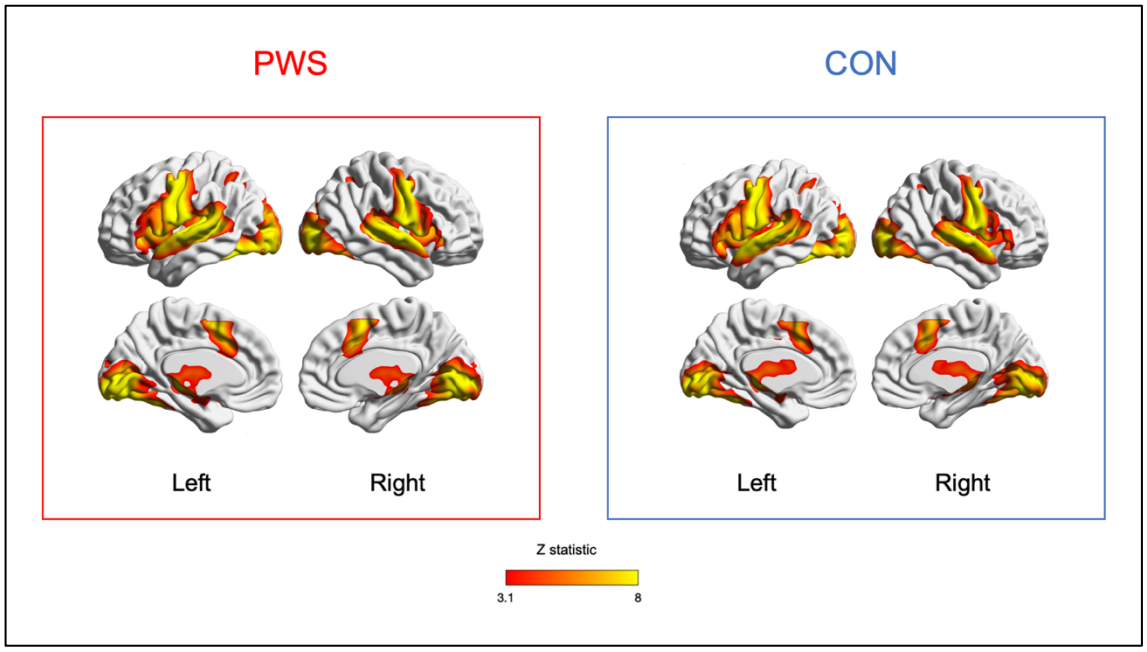



***Figure 2.01: Mean BOLD activity during sentence reading compared with baseline rest conditions for the PWS and the control groups.*** *Despite different speech fluency profiles, the patterns of brain activity were similar between the two groups. The data are represented on color-coded statistical maps, which have been thresholded at a cluster-forming Z value greater than 3.1 and a cluster extent significance level of $p < 0.05$ (PWS = 56, CON = 53). These maps are superimposed on the MNI-152/Talairach surface template. The BrainNet Viewer (Xia et al., 2013) was used to visualise the medial and lateral surfaces of both the left and right cerebral hemispheres. The left column shows the PWS group, while the right column shows the control group. PWS: People who stutter; CON: Control group.*

### 2.3.2 Group differences

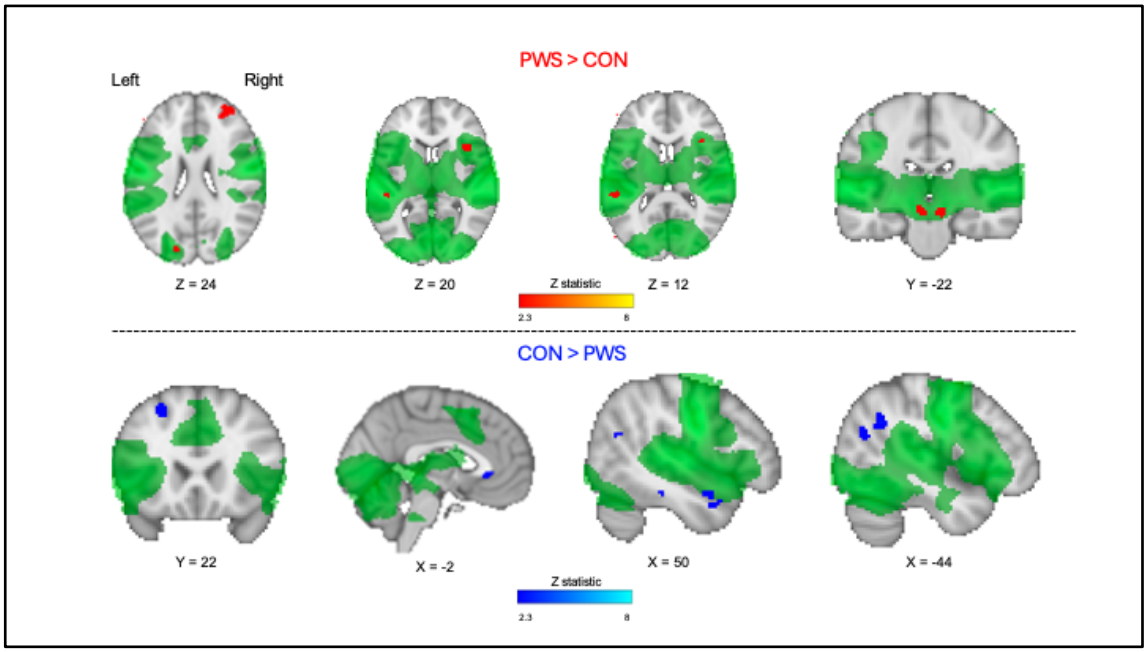



***Figure 2.02: Functional activity differences between people who stutter and controls during sentence reading.*** *Coloured maps of the Z statistic are overlaid onto the MNI-152 average brain, with a threshold of Z > 2.3. Green regions illustrate the task-positive regions against baseline. Yellow/red regions indicate areas where PWS (n = 56) had significantly more activity than controls (n = 53) while blue regions indicate areas where PWS had less activity than controls (exploratory threshold of p < .05, k > 30 voxels, uncorrected). Overactivity was observed in the right anterior superior frontal cortex, the right anterior insula extending to the frontal operculum, the left planum temporale, and the midbrain bilaterally at the level of the red nucleus. In contrast, lower activity in PWS was shown in the left superior frontal sulcus, the subgenual medial frontal cortex, the right anterior temporal lobe, and portions of the inferior parietal lobe bilaterally, including the left angular gyrus. In axial and coronal slices, the left side of the brain is shown on the left. The numbers below to each image indicate the coordinate in millimetres of that slice in x (for sagittal), y (for coronal), and z (for axial) relative to the orthogonal planes through the anterior commissure. PWS: People who stutter; CON: Control group.*

| **Brain Region** | **X** | **Y** | **Z** | **Z-statistic** |
|---|---|---|---|---|
| *PWS greater than CON* | | | | |
| Right anterior superior frontal cortex | 32 | 52 | 24 | 2.87 |
| Right anterior insula | 38 | 20 | 6 | 3.25 |
| Left planum temporale | -54 | -36 | 12 | 2.85 |
| Left red nucleus | -6 | -20 | -10 | 2.81 |
| Right red nucleus | 10 | -22 | -14 | 2.93 |
| *CON greater than PWS* | | | | |
| Left superior frontal sulcus | -24 | 22 | 50 | 2.87 |

| | | | | |
|---|---|---|---|---|
| Subgenual medial frontal cortex | -2 | 28 | -2 | 2.78 |
| Right anterior temporal lobe | 50 | 2 | -20 | 2.61 |
| Left angular gyrus | -44 | -56 | 32 | 3.09 |
| Right inferior parietal lobe | 58 | -66 | 20 | 3.17 |
| Left inferior parietal lobe | -36 | -70 | 28 | 2.75 |

***Table 2.012: Brain regions that exhibit significant differences in activity between people who stutter and controls during sentence reading.*** *The differences are identified at an exploratory threshold of p < .05 (uncorrected) with a cluster size exceeding 30 voxels. For each cluster the peak activation level, and the coordinates of the peak in MNI-152 standard space are provided. PWS = People who stutter; CON: Controls.*

During sentence reading task, different BOLD activity was observed between the PWS and controls at an exploratory threshold ($Z > 2.3$, $p < 0.5$, $k > 30$ voxels, uncorrected) (Fig. 2.2 and Table 2.2). In the PWS group, increased activity compared with controls was measured in several areas: the right anterior superior frontal cortex, the right anterior insula extending to the frontal operculum, the left planum temporale, and the midbrain at the level of the red nucleus. Conversely, areas of decreased activation in PWS included the left superior frontal sulcus, the subgenual medial frontal cortex, right anterior temporal lobe and portions of the inferior parietal lobe bilaterally, including the left angular gyrus.

## 2.4. Discussion

In the present study, we conducted an analysis combining four fMRI datasets comprising 109 participants, collected by our research group over the last decade using a consistent methodological approach and experimental task of sentence reading. This approach aimed to minimise the confounding effects encountered in individual study designs within meta-analyses (e.g., different task/baseline conditions, neuroimaging tool, methodology etc.), while leveraging a larger dataset to enhance the statistical power of our findings. Despite the sample size, our analysis did not reveal significant differences in BOLD activity in PWS compared with typically fluent controls when applying a statistical threshold corrected for multiple comparisons. To avoid a potential false negative error, we explored group differences at a lower uncorrected threshold. At this uncorrected threshold, we observed some findings aligning with previous meta-analyses

of functional imaging studies in stuttering. Greater activity was detected in the right insular cortex in PWS, which was previously identified as one of the neural "signatures" of stuttering (Brown et al., 2005). However, no significant differences between groups were observed in the cerebellum or the superior posterior temporal lobes, which were also suggested as neural signatures of stuttering (Brown et al., 2005). Subcortically, we found bilateral overactivity of red nucleus in PWS, diverging from the meta-analysis by Budde and colleagues (2014), which reported reduced activity specifically in left red nucleus. The symmetrical pattern of overactivity of this nucleus in the two hemispheres is unlikely to be a false positive result in our opinion.

Our analysis included epochs of stuttered speech, primarily to increase the statistical power of our analysis. Furthermore, literature suggests that even during perceptible fluent speech, PWS exhibit greater variability in articulation patterns compared with control subjects (Wiltshire et al., 2021; Smith et al., 2010), complicating the accurate differentiation of stuttered versus fluent speech. Although the inclusion of stuttering epochs challenges the interpretation of results as the previous research mostly analysed only the observed fluent speech, it likely provides a more representative depiction of the neural correlates associated with stuttering.

Even though we excluded the data with excessive head movements from the analysis; the disfluent state is often accompanied by head movements, potentially introducing noise into the BOLD images. This issue was addressed using a sparse-sampling design, which measures only the peak of the hemodynamic response, occurring approximately 4-6 seconds post-articulation (Hall et al., 1999). As a result, participants spoke only during silent intervals and paused during scanning, which eliminated speech-related motion during image acquisition.

Although our complete dataset included additional data involving sentence reading using fluency enhancers such as metronome-paced speech and delayed auditory feedback, we excluded these data from our analysis, similar to the methodology employed by Budde et al. (2014) in their refined data analysis. The primary rationale for this exclusion derives from findings in a previous study, which showed that activation patterns during fluency enhancement vary considerably

(Toyomura et al., 2011). These variations suggest the existence of multiple mechanisms for achieving fluency, which could potentially confound the interpretation of neural activity (Budde et al., 2014).

### 2.4.1 Overactivity in the right anterior insula/frontal operculum

In the meta-analysis of Brown and colleagues (2005), overactivity in the right anterior insula/frontal operculum (R-AI/FO) in PWS was identified as one of the neural signatures of stuttering. Subsequent meta-analysis by Budde and colleagues (2014) confirmed this finding, reporting increased R-AI/FO activations in PWS compared with controls. Furthermore, within-group analysis revealed R-AI/FO activations specifically during disfluent epochs (Kell et al., 2009; Preibisch et al., 2003; Connally et al., 2018). An fMRI study contrasting imagined speech with imagined humming conditions in PWS pointed to increased activation in right hemispheric regions, such as the right posterior IFG pars opercularis part of the frontal operculum (Neef et al., 2018). Furthermore, the study found that the severity of stuttering is associated with the strength of white matter connections in hyperactive right frontal regions, interpreting this as stuttering severity being linked to enhanced structural connectivity of the motor response inhibition network. To sum up, this overactivity in the R-AI/FO could be interpreted in various ways: potentially causing disfluency through increased inhibition, manifesting errors in speech production, or attempting to mitigate them. To further elucidate these hypotheses, employing brain stimulation techniques such as ultrasound stimulation to inhibit neural activity in the R-AI/FO in PWS, and subsequently measuring speech fluency and brain activity, could shed light in the causal relationship.

The R-AI/FO has garnered increasing recognition for its importance in articulatory functions, challenging the conventional view of Broca's area as the central coordinating center (Ackermann & Riecker, 2010; Dronkers, 1996). Studies involving macaques have shown that anterior insula stimulation triggers orofacial motor programs with emotional and communicative movements. (Jezzini et al., 2012). In humans, fMRI studies commonly report increased activation in the left anterior insula with articulation (Dronkers, 1996; Riecker et al., 2000; Wise et al., 1999).

Additionally, one study showed bilateral activation of the anterior insula during overt speech production (Bohland & Guenther, 2006) and interpreted the results as the left and right insulae function on different temporal scales in vocal control, with a significant role for the right hemisphere in managing prosodic elements of speech (Ackermann & Riecker, 2004). To better comprehend the temporal functions of the right anterior insular cortex, it would be worthwhile to review studies that have employed electrophysiological neuroimaging methods, as these provide higher temporal resolution than fMRI. A magnetoencephalography (MEG) study revealed preparatory motor activity in insular cortices approximately 160 ms after visual cues, with a right hemisphere dominance (Kato et al., 2007). This finding may indicate an autonomic role of the right insular regions in preparing for speech motor control even before the articulation starts. Research also showed the involvement of the right insular cortex in inner speech, particularly in auditory verbal imagery generation (Pratts et al., 2023). It is important to note that activation of insular regions may serve broader functions beyond articulation, potentially involving the adjustment of the autonomic system in response to respiratory demands during speech production, as suggested by a PET study showing predominantly right-lateralised activation of the mid/anterior insula during dyspnea (shortness of breath) (Banzett et al., 2000). Therefore, our observation of overactivity in the R-AI/FOI might signify differences in the planning and execution phases of overt speech production or smooth control of respiration during articulation.

The anterior insula is extensively connected with prefrontal cortical and limbic structures, such as cingulate cortex, and orbital frontal cortex (Ghaziri et al., 2017; Mesulam & Mufson, 1982). High connectivity with limbic and frontal regions underscores its central role with functions including the integration of interoceptive, exteroceptive, and emotional awareness (Simmons et al., 2013). To elucidate the role of insula in emotion processing, one study employed fMRI to investigate the association between emotional disposition and anterior insular cortex activation during participants' self-assessment of emotional and bodily states (Terasawa et al., 2013). The findings revealed positive correlations between right anterior insular activation and social anxiety. Further analyses indicated that right anterior insula activity mediated the neural correlates of

interoceptive sensibility and social fear. This is especially related in the context of stuttering, as a meta-analysis found that PWS show significantly higher levels of trait and social anxiety than controls (Craig & Tran, 2014). Although we did not directly measure fear responses in this study, it is probable that PWS experience elevated anxiety during speech production in the scanner, which could influence neural activation patterns. Therefore, the increased activity in the right anterior insular cortex we observed here in PWS might reflect these elevated anxiety levels compared with controls.

Our finding of increased activity in the right hemisphere's homologue of Broca's area, specifically the right frontal operculum, is in accordance with the hypothesis suggesting that stuttering may stem from incomplete cerebral dominance for language (Travis, 1978). This overactivity in the right hemisphere has been reported to be normalised following speech therapy (De Nil et al., 2003; Kell et al., 2009; Neumann et al., 2005). However, in Chapter 3, we investigated the theory of incomplete language lateralisation in stuttering by directly comparing activity in both hemispheres during various speech and language tasks, and found no significant differences in the proportions of PWS and controls showing left lateralisation or atypical rightwards or bilateral lateralisation (Demirel et al., 2024). Consequently, we believe that interpreting the overactivity in the R-AI/FO as indicative of reduced or atypical language laterality in PWS compared with controls is unlikely.

### 2.4.2 Lower activity in inferior parietal lobe bilaterally

The inferior parietal lobe plays a role in speech production acting as an interface between perceptual and motor systems, as part of the dorsal auditory speech processing stream (Hickok, 2009). For instance, interference with cortical stimulation over the left supramarginal and angular gyrus elicited speech difficulties, delays in verbal response, and misnaming (Van Buren et al., 1978). In the current study, the observed decrease in activity in the inferior parietal cortex bilaterally may be attributed to underlying white matter anomalies in arcuate fasciculus, which passes through the regions associated with the inferior parietal cortex and connects to the posterior superior temporal gyrus and premotor cortex (Chang et al., 2015; Neef et al., 2015; Watkins et

al., 2008b). Such structural abnormalities could potentially disrupt the signal transmission between these neural pathways essential for integrating articulatory planning and sensory feedback. An fMRI study investigating the brain activity during imagined speech and imaging humming tasks found activation in the left posterior-dorsal area 44, which is coupled with the left inferior parietal lobule in fluent speakers; however, this activation was missing in PWS in both conditions interpreted as a deficiency in the structural connectivity of the left superior longitudinal fasciculus (Neef et al., 2016). The absence of functional connectivity in the parietal lobules observed in this study was located anterior (x = -54, y = -36, z = 22) to the region where we detected reduced activity (x = -44, y = -56, z = 32). It is important to note that, although the majority of previous structural and functional studies have reported differences in the left hemisphere, particularly in the connections between the left parietal lobule and the left premotor and motor areas, we observed reduced activity bilaterally in the inferior parietal lobe. Increased activity in the inferior parietal cortex bilaterally linked to increased fluency (Budde et al., 2014; Neef et al., 2015) highlights the importance of integrative processes across both hemispheres for fluent speech production.

### 2.4.3 Asymmetrical activity in frontal regions

We observed asymmetrical frontal lobe activity, specifically elevated activity in the right anterior frontal cortex and decreased activity in the left superior frontal sulcus (L-SFS) during sentence reading tasks. This pattern aligns with known asymmetrical activity between hemispheres in stuttering, although it somewhat diverges from previous literature, which predominantly identified asymmetries within more posterior regions compared with our findings, including inferior frontal, premotor, and primary motor areas (Belyk et al., 2017; Neef et al., 2018; Watkins et al., 2008).

The reduced activation of the L-SFS in PWS is particularly intriguing, given the established role of the left dorsolateral prefrontal cortex (L-DLPFC), of which the L-SFS is a part, in improving working memory capacity, top-down attentional control, and executive functions (Brosnan & Wiegand, 2017; Edin et al., 2009; Mansouri et al., 2009). L-DLPFC has connections with both

auditory and motor regions (Romanski et al., 1999; Selemon & Goldman-Rakic, 1988). One MEG study showed that Alzheimer's disease patients exhibited abnormal sensorimotor integration during an altered auditory feedback task by showing reduced left prefrontal activity (Ranasinghe et al., 2019). Another study using theta-burst stimulation to inhibit L-DLPFC in healthy young adults supported its role in sensorimotor integration in speech (Liu et al., 2020). The results showed significantly larger vocal compensations in response to altered auditory feedback in the inhibitory stimulation condition compared with the sham condition, suggesting that the L-DLPFC exerts inhibitory control over compensatory behaviours and is essential for detecting and correcting discrepancies between intended and actual vocal output.

Thus, the observed hypoactivity in the L-SFS among PWS could reflect a diminished capacity for inhibitory control over sensorimotor control of speech production. This interpretation is supported by the control theory, which posits that excessive compensatory adjustments needs to be under inhibitory control otherwise it can destabilise speech motor control systems (Houde & Nagarajan, 2011). To explain our findings in asymmetry, specifically the increase activity over the right anterior frontal cortex, it is worth mentioning a study with Parkinson's disease patients who underwent comprehensive voice therapy (Narayana et al., 2010). This study reported enhanced activation in the R-DLPFC post-treatment, which correlated with increased vocal volume in Parkinson's disease patients. Therefore, the increased activity of the right anterior frontal cortex observed in our results may represent an attempt to bolster inhibitory control over speech production in PWS to achieve more stable articulation.

Contrary to the compensation interpretation of the R-DLPFC to achieve more stable articulation, overactivity in the R-DLPFC of PWS might indicate error monitoring and/or inhibition of speech motor command initiation (Jackson et al., 2022; Kell et al., 2009; Lu et al., 2009; Neef et al., 2018). In a clinical context, therapeutic interventions such as fluency shaping have been documented to decrease R-DLPFC activity transiently, which is correlated with a reduction in stuttering symptoms and provides a neurobiological framework for understanding the mechanisms of stuttering alleviation (De Nil et al., 2003b; Neumann et al., 2005). In a novel

study, Jackson et al. (2022) used a delayed-response task to measure hemodynamic activity with functional near-infrared spectroscopy (fNIRS) to investigate the role of the R-DLPFC during stuttering anticipation. The study found that PWS showed higher activation in the R-DLPFC than fluent speakers during the five seconds preceding speech. Additionally, PWS exhibited greater activity in this brain region for stuttered versus fluent utterances, and for anticipated (words that the person expects to stutter on) versus unanticipated words. This suggests that R-DLPFC overactivity may play a role in error-likelihood monitoring and action-stopping mechanisms during stuttering anticipation. It is important to note that the pre-speech stuttering anticipation phase was not the focus of our study yet it is probable that the PWS showed higher activity in the R-DLPFC during sentence reading due to stuttering anticipation as we included stuttered utterances in our analysis. Overall, the overactivity observed in the R-DLPFC in our PWS group may tentatively be interpreted as reflecting increased neural engagement in error likelihood monitoring or action-stopping processes.

This asymmetrical activity pattern in frontal lobes may open avenues for targeted interventions, such as using non-invasive brain stimulation of the DLPFC. In previous research, excitatory repetitive transcranial magnetic stimulation to the L-DLPFC improved subjective voice-related quality of life in Parkinson's disease patients (Dias et al., 2006). Another promising avenue for research could involve using inhibitory non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), to inhibit overactivity in the R-DLPFC. This approach could also help test the hypothesis that increased R-DLPFC activity is linked to heightened error detection and action stopping.

### 2.4.4 Overactivity in red nucleus

The red nucleus contributes to motor control and evolutionary adaptations to varying motor demands across different species. In humans, our understanding of the connections of this nucleus primarily comes from region of interest-based resting-state fMRI analyses (Nioche et al., 2009; Zhang et al., 2015). A recent resting-state fMRI study described an extensive red nucleus functional connectivity network, including regions such as basal ganglia and insula (Zhang et al.,

2015), which have been reported as important brain regions in stuttering (Watkins et al., 2008; Brown et al., 2005; Chang & Guenther, 2020; Theys et al., 2024). Task fMRI studies with healthy participants have reported stronger activity in the red nucleus during the preparation of self-initiated finger movements compared with externally triggered movements (Boecker et al., 2008; Cunnington et al., 2002). For instance, one study reported increased activity during the planning phase of the internally initiated finger movement condition, as opposed to the externally triggered condition (Boecker et al., 2008). This increased activity was also observed in the frontal regions, including the DLPFC, inferior parietal regions, and insula, which align with the differences in activation we observed in PWS during our self-initiated sentence reading task. Therefore, one possible interpretation could be that the increased activity in red nucleus during the planning phase of self-initiated motor movements might represent the heightened effort required to execute speech motor commands during sentence reading.

In chronic post-stroke patients, strengthening of the cortico-rubro-spinal system, encompassing red nucleus, may serve as a compensatory mechanism for pyramidal tract damage, thereby aiding motor recovery. This hypothesis is substantiated by observed correlations between fractional anisotropy (FA) values, a metric for white matter integrity, and motor function assessments, indicating that enhanced integrity in this pathway correlates with improved motor performance (Rüber et al., 2012). Specifically, increased FA in the red nucleus, rubrospinal, and cortico-red nucleus tracts have been positively correlated with the level of motor impairment in chronic post-stroke patients at various intervals post-lesion, suggesting plasticity of this region to compensate for the affected pyramidal tracts (Jang & Kwon, 2015; Kim et al., 2018; Rüber et al., 2012). In stuttering, it is possible that the red nucleus plays a compensatory role in response to structural differences in basal ganglia (Watkins et al., 2008; Wu et al., 1997; Theys et al., 2024), which are considered key structures involved in self-initiated motor movements and are implicated in causing disfluencies (Alm, 2004a; Burghaus et al., 2006a; Chang & Guenther, 2020). It is important to note that our findings diverge from those of Budde and colleagues (2014), who identified reduced activity specifically in the left red nucleus during fluent speech in PWS. While

the role of red nucleus in stuttering is not well understood, it is likely involved as a compensatory agent for self-initiated movements, contributing to the complex neurobiological mechanisms underlying the disorder.

## 2.5. Limitations and future directions

Our study has several limitations that must be considered when interpreting the findings. Firstly, we observed sub-threshold differences in activity in brain regions critical for self-initiated motor commands, such as the left superior frontal regions, anterior insula/frontal operculum, and red nucleus. However, interpreting these results is challenging due to the inherently low temporal resolution of fMRI. This limitation restricts our ability to precisely map the dynamic processes involved in speech production and stuttering. Electrophysiological studies suggest that stuttering involves differences in neural oscillations in beta and other frequency bands in both children (Etchell et al., 2016; Özge et al., 2004) and adults (Joos et al., 2014; Kikuchi et al., 2017; Mersov et al., 2016; Mock et al., 2016; Orpella et al., 2024; Saltuklaroglu et al., 2017; Sengupta et al., 2016). Specifically, PWS show exaggerated beta desynchronisation during movement preparation and execution relative to controls (Mersov et al., 2016), and the intensity of the beta desynchronisation can predict stuttered utterances (Orpella et al., 2024). Future research will utilise high-resolution brain stimulation techniques such as ultrasound brain stimulation to explore the causal roles of these aberrant activities, whether they are inhibitory, compensatory or error detecting. These methods could also identify therapeutic targets, enabling interventions that convert stuttered speech into fluent utterances before articulation begins.

Secondly, the ecological validity of using a sentence reading task to study stuttering is limited. Stuttering is more likely to occur during spontaneous information transfer in natural conversational settings rather than in isolated reading tasks (Jackson et al., 2021). Future studies may aim to enhance ecological validity by incorporating AI-driven conversational agents during scanning. This approach would facilitate real-time interactions, more closely mirroring everyday communication and potentially providing deeper insights into the neural correlates of stuttering.

Lastly, it is worth mentioning the potential for methodological confounds that may bias findings towards false negatives. Individual variability in neural activity among PWS, such as differences in stuttering severity or compensatory strategies, may mask region-specific effects at the group level. Additionally, the sparse sampling design, although effective at reducing movement-related noise and capturing the haemodynamic response peak, limits temporal resolution and may overlook transient BOLD activity. Finally, while our sample size is robust, detecting subtle differences may require analyses tailored to specific brain regions. Future studies could mitigate these potential biases by incorporating regions of interest analyses based on prior meta-analyses, though this approach could introduce its own bias by focusing on known regions at the expense of novel findings.

## 5. Conclusion

In this combined analysis of four fMRI studies, we investigated the neural correlates of stuttering, using a large sample and a consistent methodological approach and task of sentence reading. Although group differences in task-evoked activity did not remain significant after correction for multiple comparisons, we observed some results at a lower uncorrected threshold that were consistent with earlier meta-analyses of functional imaging studies in stuttering. For example, we found increased activation in the right anterior insular cortex, reaffirming its role as a neural marker of stuttering, and bilateral overactivation in the red nucleus of PWS, suggesting a compensatory mechanism for disruptions in the speech motor pathway. Additionally, we observed asymmetrical frontal activity between hemispheres, with elevated activity in the right anterior frontal cortex and decreased activity in the left superior frontal sulcus, along with reduced activation in the inferior parietal cortex bilaterally, suggesting disruptions in the integration of articulatory planning and sensory feedback. These findings highlight the complex neurobiological mechanisms underlying stuttering, involving both cortical and subcortical regions. While our study advances the understanding of the neural correlates of stuttering, it also emphasises the need for further research to explore these differences in a causally and to develop targeted interventions that can effectively address the neural differences associated with stuttering.

# 3

# No evidence of altered language laterality in people who stutter across different brain imaging studies of speech and language


## Abstract

A long-standing neurobiological explanation of stuttering is the incomplete cerebral dominance theory, which refers to competition between two hemispheres for "dominance" over handedness and speech, causing altered language lateralisation. Renewed interest in these ideas came from brain imaging findings in people who stutter of increased activity in the right hemisphere during speech production or of shifts in activity from right to left when fluency increased. Here, we revisited this theory using functional MRI data from children and adults who stutter, and typically fluent speakers (119 participants in total) during four different speech and language tasks: overt sentence reading, overt picture description, covert sentence reading and covert auditory naming. Laterality indices were calculated for the frontal and temporal lobes using the Lateralisation Index toolbox running in Statistical Parametric Mapping. We also repeated the analyses with more specific language regions, namely the pars opercularis (Brodmann Area 44) and pars triangularis (Brodmann Area 45). Laterality indices in people who stutter and typically fluent speakers did not differ and Bayesian analyses provided moderate to anecdotal levels of support for the null hypothesis (i.e., no differences in laterality in people who stutter compared with typically fluent speakers). The proportions of the people who stutter and typically fluent speakers who were left lateralised or had atypical rightwards or bilateral lateralisation did not differ. We found no support for the theory that language laterality is reduced or differs in people who stutter compared with typically fluent speakers.

## 3.1 Introduction

Persistent developmental stuttering is a speech fluency disorder affecting approximately 1% of people worldwide that appears to occur in all languages. The onset of stuttering is typically between ages 2 and 4 years (Yairi & Ambrose, 2013), which corresponds with the rapid development of language skills, such as increase in the average length of utterance (Zackheim & Conture, 2003). The occurrences of stuttering are highly variable both within and across individuals. For example, the frequency of stuttered syllables is affected by different factors, including the complexity of grammar and the length of the planned utterance (Howell et al., 1999; Logan & Conture, 1995; Zackheim & Conture, 2003). Language proficiency is typically unaffected in people who stutter (PWS) (Reilly et al., 2009; Yairi & Ambrose, 1999); PWS know what they want to say, but the flow of speech is disrupted by repetitions, prolongations, and blocks.

Language is perhaps the most lateralised cognitive function: showing primarily left hemisphere involvement for around 96% of right-handers and 70% of left-handers; whilst the rest, 4% of right-handers and 30% of left-handers have what is called atypical lateralisation, indicating either bilateral or primarily right hemisphere involvement (Rasmussen & Milner, 1977). The underlying neurophysiology of stuttering is not yet fully understood, however, one popular neurological explanation of stuttering is the incomplete cerebral dominance theory, which suggests altered patterns of hemispheric specialisation and competition between hemispheres for "dominance" over handedness and speech (Orton, 1927; Travis, 1978). Although scientific interest in the incomplete cerebral dominance theory in stuttering declined over recent decades, it persists as an explanation frequently given by PWS themselves. For example, some PWS describe themselves as being naturally left-handed, but due to the forced use of the right hand, say on school entry, they started to stutter. It is argued that excessive use of the nondominant hand weakens the dominant hemisphere over time. This can cause conflict between hemispheres, leading to altered language lateralisation, which refers to the dominance of one cerebral hemisphere over the other in managing language functions (Orton, 1927).

The first functional neuroimaging meta-analysis in stuttering appeared to support the incomplete cerebral dominance theory by suggesting a tendency towards rightward lateralisation in PWS relative to controls during speech production tasks (Brown et al., 2005). Overactivation in the right inferior frontal cortex is commonly reported in stuttering during speech production tasks, particularly activity of the right frontal operculum and anterior insula (Neef et al., 2018; Watkins et al., 2008a) extending to the orbitofrontal cortex (Kell et al., 2009). Moreover, the overactivity in the right hemisphere is described as being "normalised" with speech therapy resulting in typical left lateralised activity (De Nil et al., 2003; Kell et al., 2009; Neumann et al., 2005). Patterns of activity and timing of responses in auditory networks during passive listening tasks also differ between PWS and controls (Beal et al., 2011; Cai et al., 2012; Sato et al., 2011; Weber-Fox & Hampton, 2008). Sato and colleagues (2011) using near-infrared spectroscopy documented diverse laterality in PWS during passive listening to pairs of syllables that included either a phonemic or prosodic contrast, which typically produce left- and right-lateralised patterns of activity respectively in fluent speakers (Sato et al., 2011). Notably, none of the adults, school-aged children or pre-school children who stuttered showed significant expected patterns of lateralization for either phonemic or prosodic contrasts, and some showed the reverse pattern.

Even though there are consistent findings of overactivity in the right hemisphere in the functional imaging literature, it still needs to be clarified whether these findings reflect an altered pattern of lateralization. To demonstrate this, it is necessary to statistically compare activity in the two hemispheres during different speech and language tasks. This approaches typically uses a laterality index (LI) calculated using the formula LI = (L-R) / (L+R) to compare the functional activity between two hemispheres. Positive LIs indicate leftwards lateralisation and negative LIs indicate rightwards lateralisation and LIs between $-0.2 \leq LI \leq 0.2$ indicate weak lateralisation, sometimes called "bilateral" (Wilke & Lidzba, 2007). The values entered into the formula for the left and right hemispheres reflect the amount of activity in a given brain region. This is expressed as percent signal change from a baseline or other contrast, or in terms of the number of activated voxels above a certain threshold. This threshold is sometimes referred to as "activated tissue

volume," or it can be the sum of the values of these voxels, which is typically a statistic that reflects the strength of a voxel's correlation with the task. LIs calculated in this way from brain imaging data can be strongly influenced by individual differences in brain activation and noise levels, the statistical threshold employed, and statistical outliers (Wilke et al., 2006). For example, above a particular threshold, no active voxels might remain in the nondominant hemisphere leading to LI = 1 for the dominant hemisphere, which is biologically implausible. The LI toolbox (Wilke & Lidzba, 2007) running in SPM (Statistical Parametric Mapping: www.fil.ion.ucl.ac.uk/spm/software/spm12/) avoids threshold dependency by calculating LI values across multiple threshold levels and uses a bootstrapping approach to reduce the effect of outliers. The LI toolbox has been successfully employed to measure laterality because of these advantages (Bradshaw et al., 2017).

To address the incomplete cerebral dominance theory in stuttering, we calculated laterality indices for four different speech and language tasks performed using functional MRI in PWS and typically fluent speakers (TFS). Our analyses of these laterality indices were used to target two main questions: (1) Are there any differences between PWS and TFS in functional lateralisation across speech and language tasks? (2) Does functional lateralisation vary across tasks in PWS or TFS or both?

## 3.2 Methods

### 3.2.1 Participants

We combined data from a several cohorts of children and adults who stutter who were scanned over the past decade using fMRI during different speech and language tasks. Following exclusion for excessive movement during scanning (details below), useable data were available in 119 participants, 61 PWS (*M*age = 29 years, range = 14-54 years), and 58 TFS (*M*age = 28 years, range = 14-53 years). The groups were not significantly different in terms of age: $t(117) = 0.60$, $p = 0.55$. Chi-squared analysis showed that the groups did not differ in terms of the distribution of handedness ($\chi 2 = 2.23$, $p = 0.13$) or gender ($\chi 2 = 2.22$, $p = 0.14$). One study with 38 participants

(23 PWS, 15 TFS) included only right-handed male participants, therefore we repeated the chi-squared analysis assessing the distribution of handedness after excluding data from this study and again found no difference between groups in terms of the distribution of handedness ($\chi 2 = 3.40$, $p = 0.06$). For the PWS group, stuttering ranged in severity from very mild to very severe (9 – 46, median 26) according to the Stuttering Severity Instrument (SSI) (Glyndon D. Riley., 1994). At the time of the scan, stuttering severity was assessed as very mild in 8, mild in 11, moderate in 25, severe in 11, and very severe in 6 PWS. The largest subset of participants had performed one of four slightly different versions of overt sentence reading: 56 PWS, and 53 TFS. Smaller subsets had completed tasks involving overt picture description (16 PWS and 18 TFS) and two covert speech tasks involving sentence reading (12 PWS and 12 TFS) and auditory naming (12 PWS and 16 TFS). Table 3.1 shows the distribution of handedness and sex between groups.

| *Handedness, Gender, and Age* | **PWS** | | | | | | **TFS** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Handedness** | | **Gender** | | **M age** | **N** | **Handedness** | | **Gender** | | **M age** |
| | | **L** | **R** | **W** | **M** | | | **L** | **R** | **W** | **M** | |
| Overt sentence reading | 56 | 7 | 49 | 10 | 46 | 28 | 53 | 2 | 51 | 13 | 40 | 28 |
| Overt picture description | 16 | 2 | 14 | 4 | 12 | 30 | 18 | 2 | 16 | 5 | 13 | 32 |
| Covert sentence reading | 12 | 3 | 9 | 3 | 9 | 30 | 12 | 1 | 11 | 3 | 9 | 29 |
| Covert auditory naming | 12 | 3 | 9 | 3 | 9 | 30 | 16 | 1 | 15 | 6 | 10 | 27 |

***Table 3.01: Distribution of handedness and sex of groups across tasks.*** *PWS: people who stutter; TFS: typically fluent speakers; L: Left; R: Right; W: Women; M: Men; Mage: Mean age (in years).*

### 3.2.2 Tasks

The tasks analysed included overt sentence reading, combined from different studies that have been conducted in our laboratories, overt picture description, covert sentence reading, and covert auditory naming tasks. Overt speech refers to audible production of words/sentences, while covert speech refers to silent production of words/sentences with no articulation. A sparse sampling design (Hall et al., 1999) was used in the overt speaking tasks, in which participants spoke during the silent period between scans. This ensures that the imaging data are not confounded with speech-movement-related artefacts and reduces the possible fluency-enhancing effect of the scanner noise. It also allowed participants to hear the speech they produced. In contrast, continuous acquisition protocols of typical echo-planar imaging were used for the covert speech tasks. Details of the scanners used, and scanning parameters are provided in Supplementary Materials with reference to published versions of these studies.

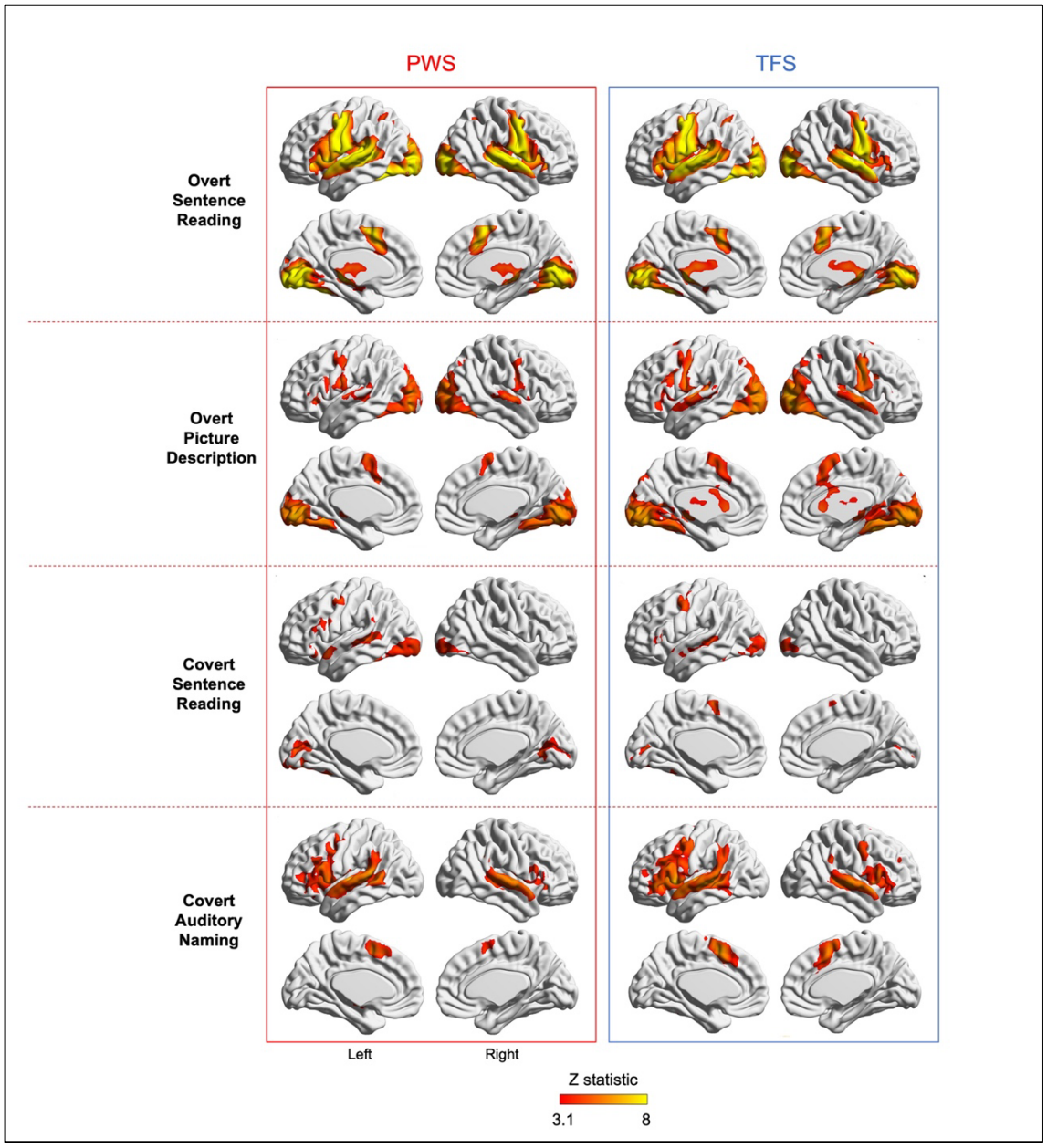



***Figure 3.01: Average brain activity for groups of PWS and TFS during four different tasks.*** *Patterns of brain activity were similar in the two groups. The coloured statistical maps are of Z-statistic images thresholded using clusters determined by Z > 3.1 and a corrected cluster significance threshold of P = 0.05 overlaid on the MNI-152/Talairach surface template using BrainNet Viewer (Xia et al., 2013). Medial and lateral surfaces of the left and right hemispheres are shown. PWS: people who stutter are on the left of the image; TFS: typically fluent speakers are on the right. The sample sizes for each task were as follows: overt sentence reading: PWS = 56, TFS = 53; overt picture description: PWS = 16, TFS = 18; covert sentence reading: PWS = 12, TFS = 12; covert auditory naming: PWS = 12, TFS = 16.*

**3.2.2.1 Overt Sentence Reading:** During all versions of the sentence reading task, participants saw a sentence printed in white on a black screen. In some participants (34), a scene corresponding to the sentence was also visible. All participants read the sentence out loud and could hear themselves speaking over headphones during the silent intervals between scan measurements.

The baseline conditions consisted of viewing a row of letter X's that replaced all other letters in a sentence (37 participants), or sentences written in the Farsi alphabet (38 participants), which was unreadable by participants, or a fixation cross (34 participants). Activity during sentence reading was contrasted with the baseline to reveal the brain areas involved in reading aloud, which involves visual word recognition, semantic and syntactic processing, phonological assembly, speech articulation, and monitoring of self-produced speech.

**3.2.2.2 Overt Picture Description:** The task was to describe a picture that appeared on the screen using the participant's own words and spoken out loud. As for overt sentence reading, participants could hear their speech during the silent intervals between scans. The task required conceptualization of the scene, lexical selection and retrieval, phonological and syntactic planning, speech articulation, and monitoring of self-produced speech. A fixation cross was used as a baseline for the picture description task (Connally et al., 2018).

**3.2.2.3 Covert Sentence Reading:** Participants read sentences in their imagined speech. In contrast to the overt sentence reading task, reading a sentence covertly does not involve execution of articulatory movements or sensory feedback. This task was contrasted with a row of Xs presented on the screen.

**3.2.2.4 Covert Auditory Naming:** Participants heard a short phrase (e.g. "bees make it" over headphones and were asked to generate a word in response (e.g. "honey") in their imagined speech. The task requires decoding the phonological and semantic information of the auditory input, lexical search and retrieval, and phonological form encoding to generate a word associated with the semantic description (Badcock et al., 2012). A silent baseline and reversed speech baseline conditions were used for the auditory naming task.

### 3.2.3 fMRI Data Analysis

The fMRI data were analysed at the single-subject level using FEAT (FMRI Expert Analysis Tool part of the FMRIB Software Library) (Woolrich et al., 2001). The echo-planar images were motion corrected, smoothed using an 8-mm full-width at half-maximum smoothing kernel,

undistorted using fieldmaps where available and registered to the individual's T1-weighted structural image using boundary-based registration. These individual T1-weighted images were then registered to the MNI-152 template using FMRIB's non-linear registration tool (FNIRT embedded in FSL). The six motion regressors from the motion correction were included as covariates of no-interest. For continuous imaging sequences (the two covert tasks), the task design was convolved with the double-gamma haemodynamic response function and temporal derivatives were included in the general linear model. For sparse-sampling sequences, convolution with the haemodynamic response function and temporal derivatives were turned off.

Data from five additional scans from the PWS group were excluded from further data analysis due to excessive head movements during scanning. Exclusion criteria were set concerning the mean displacements of head movements being larger than the widest voxel dimension (i.e., > 4 mm) relative to subsequent time points or a warning from the MCFLIRT motion correction tool (Jenkinson et al., 2002) concerning high levels of motion.

### 3.2.4 Quantifying Laterality Indices

The statistical maps for individual participants were registered to the MNI-152 standard space using their individual T1-weighted structural images (see above) and transferred to the Statistical Parametric Mapping software (http://fil.ion.ucl.ac.uk/spm/) for use with the Laterality toolbox (Wilke et al., 2006). The LI toolbox uses a weighted bootstrapping algorithm to create LI values from the fMRI data by obtaining voxel values for both the left and right hemispheres. First, a vector of voxel values is created from the masked and thresholded input image. Then the algorithm resamples the voxel values 100 times each from the left and right regions of interest (ROIs). All possible LI combinations are calculated from these samples 10,000 times. This procedure is repeated for 20 different threshold intervals (from 0 to the maximum threshold value). Finally, all LIs are plotted on a histogram, and only the central 50% is used as the final LI measure to reduce the influence of outliers. In addition, the LI toolbox produces a weighted mean from the results obtained at different thresholds, which ensures that voxels showing a higher

correlation with the task have more impact on the result. Therefore, LI values acquired at a higher threshold are given more weight in the final LI-weighted mean value.

ROIs were chosen based on masks of the frontal and temporal lobes, as these include the regions typically activated by the language tasks. Activity from voxels in the medial wall was excluded from the LI calculations since it is difficult to determine the hemispheric origin of activity at this location due to smoothing (standard exclusion mask: midline -5 mm). In separate analyses, we also measured the LI values in smaller ROIs, namely the pars opercularis (BA44) and pars triangularis (BA45) of the inferior frontal gyrus, to provide a more granular analysis. Masks were generated using the Julich Atlas within FSL software, for the BA44 and BA45 brain regions with a threshold set at 30%.

### 3.2.5 Statistical Analysis

Initial inspection of the data suggested no group differences in terms of laterality indices (see Fig. 2 below); therefore, we selected a Bayesian approach in order to weigh the evidence in favour of the null relative to the alternative hypothesis. We performed Bayesian t-tests to address our first research question to test whether there are differences in LI-weighted values between PWS and the TFS group for four different speech and language tasks. We reported the Bayesian Factor 01 value, which refers to the ratio of the 'likelihood of data given the null hypothesis / likelihood of data given the alternative hypothesis. In alignment with Jeffreys' guidelines (Jeffreys, 1939), we considered a Bayes factor falling within the range of 1 to 3 as indicative of anecdotal evidential support, while a Bayes factor ranging from 3 to 10 signifies a moderate level of evidential support. A Bayes factor surpassing 10, on the other hand, indicates robust evidential support. We also categorized datasets as showing typical patterns of leftwards laterality (> 0.2) compared with atypical (< -0.2 right or bilateral, -0.2 to 0.2 LIs), to determine whether the distribution of laterality in individuals differed between groups using chi-squared analysis.

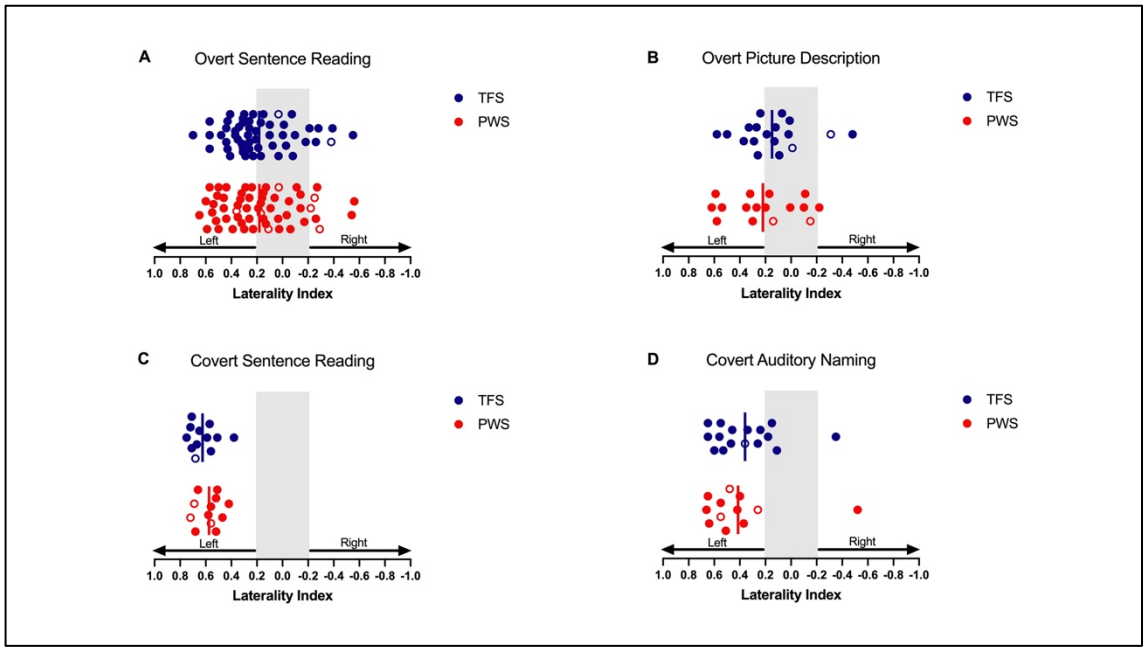



***Figure 3.02: Laterality indices in PWS and TFS based on activity in the frontal lobes. Solid vertical lines represent group means.*** *The grey area represents LI values between −0.2 and 0.2, which are considered not lateralized. PWS: people who stutter; TFS: typically fluent speakers. The open circles indicate left-handedness in both groups. We performed Bayesian t-tests to test the differences in LI-weighted values between PWS and TFS across four different speech and language tasks. The Bayesian independent samples t-tests yielded a BF in favour of the null hypothesis of* ***(A)*** *4.92 for overt sentence reading (PWS = 56, TFS = 53),* ***(B)*** *2.41 for overt picture description (PWS = 16, TFS = 18),* ***(C)*** *1.55 for covert sentence reading (PWS = 12, TFS = 12) and* ***(D)*** *2.56 for covert auditory naming (PWS = 12, TFS = 16) tasks.*

To compare laterality indices among the different tasks, linear mixed model regression analyses were performed. All Bayesian and chi-squared tests were carried out using the software JASP (JASP Team, 2022) and we used RStudio (RStudio Team, 2020) to perform linear mixed model regression analyses.

## 3.3 Results

### 3.3.1 Brain activity during tasks: Group Averages

We looked at the brain activity of each group relative to the baseline condition for each task based on a cluster-forming threshold of $Z > 3.1$ and an extent threshold of $p < .05$ (corrected for family-wise error). Both groups showed a broad range of activity in brain regions expected to be activated by speech and language (Fig. 3.1; Table 3.2).

During the overt sentence reading task, large portions of the primary motor cortex, premotor cortex, presupplementary motor area extending to anterior cingulate cortex, superior temporal

lobe, the thalamus, ventral occipito-temporal cortex, and lobule VI of the cerebellum were significantly activated bilaterally in the PWS group but somewhat more extensively on the left. The TFS group exhibited strikingly similar brain activity patterns to the PWS group.

The overt picture description task evoked significant activity in premotor and primary motor cortex, the presupplementary motor area, superior temporal gyrus, thalamus, ventral occipito-temporal cortex, and the anterior lobe of the cerebellum, all bilaterally with additional activation of the left inferior frontal gyrus in both groups that was more extensive in the TFS group.

The covert sentence reading task evoked significant activity in inferior frontal cortex, primary motor cortex (at the level of the face representation), superior temporal gyrus, and mid fusiform gyrus in the left hemisphere, and in lateral and medial occipital cortex bilaterally in both groups. There was additional activity in the cerebellar vermis in PWS and presupplementary motor area in the TFS group.

During the covert auditory naming task, there was significant activity in the inferior frontal gyrus bilaterally but more extensively on the left, the presupplementary motor area, the superior temporal gyrus and dorsal striatum bilaterally, and in the right anterior and posterior lobes of the cerebellum in both groups. In the PWS, there was significant activity in the primary motor cortex on the left and this was seen bilaterally in the TFS group; TFS also had activity in the left anterior lobe of the cerebellum.

### 3.3.2 LIs based on task-evoked activity in the frontal lobes

#### 3.3.2.1 Overt Sentence Reading Task

The results of our LI calculations for the frontal lobe masks for the sentence reading task are shown in Table 3.2 and Fig. 3.2. The sentence reading task was completed by the largest number of participants combined across four different versions of the task. A Bayesian independent samples t-test (two-sided) revealed a Bayes factor of 4.92, indicating moderate evidence in support of the null hypothesis (LIs are similar between PWS and TFS groups) rather than the alternative hypothesis (LIs differ between PWS and TFS). Chi-squared statistics found that the

number of individuals in each group who showed the typical pattern of leftwards laterality compared with atypical (right or bilateral LIs) did not differ ($\chi^2 = 0.79$, $p = 0.37$; see Table 3.2). It is worth noting that the mean LI for each group falls in the range considered indicative of weak laterality or bilateral (Table 3.2), indicating that the tasks is not reliably strongly lateralized, though individual values ranged from -0.56 to 0.65 in PWS and -0.55 to 0.70 in TFS.

| *Region* x Task | PWS | | | | TFS | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean LI + SEM | Typ | Atyp | N | Mean LI + SEM | Typ | Atyp |
| *Frontal lobes* | | | | | | | | |
| Overt sentence reading | 56 | 0.18 ± 0.03 | 28 | 28 | 53 | 0.18 ± 0.03 | 31 | 22 |
| Overt picture description | 16 | 0.21 ± 0.07 | 9 | 7 | 18 | 0.14 ± 0.06 | 8 | 10 |
| Covert sentence reading | 12 | 0.57 ± 0.02 | 12 | 0 | 12 | 0.62 ± 0.03 | 12 | 0 |
| Covert auditory naming | 12 | 0.41 ± 0.09 | 10 | 2 | 16 | 0.36 ± 0.06 | 12 | 4 |
| | | | | | | | | |
| *Temporal lobes* | | | | | | | | |
| Overt sentence reading | 56 | 0.12 ± 0.04 | 29 | 27 | 53 | 0.13 ± 0.04 | 24 | 29 |
| Overt picture description | 16 | -0.06 ± 0.06 | 4 | 12 | 18 | 0.00 ± 0.05 | 6 | 12 |
| Covert sentence reading | 12 | 0.56 ± 0.06 | 12 | 0 | 12 | 0.58 ± 0.04 | 12 | 0 |
| Covert auditory naming | 12 | 0.23 ± 0.08 | 9 | 3 | 16 | 0.24 ± 0.05 | 11 | 5 |
| | | | | | | | | |
| *BA 44* | | | | | | | | |
| Overt sentence reading | 56 | 0.18 ± 0.05 | 30 | 26 | 53 | 0.20 ± 0.05 | 28 | 25 |
| Overt picture description | 16 | 0.40 ± 0.07 | 12 | 4 | 18 | 0.34 ± 0.07 | 13 | 5 |
| Covert sentence reading | 12 | 0.59 ± 0.03 | 12 | 0 | 12 | 0.51 ± 0.09 | 11 | 1 |
| Covert auditory naming | 12 | 0.50 ± 0.08 | 11 | 1 | 16 | 0.41 ± 0.06 | 14 | 2 |
| | | | | | | | | |
| *BA45* | | | | | | | | |
| Overt sentence reading | 56 | 0.04 ± 0.06 | 24 | 32 | 53 | 0.13 ± 0.05 | 25 | 28 |
| Overt picture description | 16 | 0.34 ± 0.11 | 12 | 4 | 18 | 0.19 ± 0.09 | 10 | 8 |
| Covert sentence reading | 12 | 0.51 ± 0.09 | 11 | 1 | 12 | 0.45 ± 0.11 | 10 | 2 |
| Covert auditory naming | 12 | 0.43 ± 0.09 | 10 | 2 | 16 | 0.40 ± 0.10 | 14 | 2 |
| | | | | | | | | |

***Table 3.02:Laterality indices across tasks for the frontal and temporal lobes, BA44 and BA45.*** *LI: Laterality indices' weighted mean; SEM: Standard Error of Mean; Typ: Participants who show typical pattern of leftwards laterality; Atyp: Participants who show right or bilateral laterality.*

### 3.3.2.2 Overt Picture Description, Covert Sentence Reading, Covert Auditory Naming

In different subsets of the overall sample, we also analysed LIs for the overt picture description task, covert sentence reading task, and covert auditory naming task (Table 3.2, Fig. 3.2). Bayesian independent samples t-test analyses revealed Bayes factors of 2.41, 1.55, and 2.56, respectively for these tasks, indicating anecdotal evidence in support of the null hypothesis (no group

differences for each task). On the basis of these findings in smaller subsets of the sample, we can neither reject nor support the null hypothesis. Chi-squared analyses found no group differences regarding the number of typically or atypically lateralised individuals in the overt picture description task ($\chi^2 = 0.47$, $p = 0.49$), covert sentence reading task (all participants were left lateralised) and covert auditory naming task ($\chi^2 = 0.28$, $p = 0.59$).

#### 3.3.2.3 Laterality Effect of Different Tasks

Inspection of Fig. 3.2 indicates that, for the frontal lobes, the two covert tasks (covert sentence reading and auditory naming) were more robustly lateralized at both the group and the individual level relative to the pattern of lateralization seen for the overt tasks (overt sentence reading and picture description). To test this quantitatively, we employed linear mixed models with overt tasks as a fixed effect. Group (PWS and TFS) was entered into the model as interactions for this fixed effect with intercepts of subjects as our random effect. The model revealed that LIs were significantly more left lateralised for covert tasks (N = 51, LI = 0.49, *SE* = 0.03) compared with overt tasks (N = 143, LI = 0.18, *SE* = 0.02) ($\beta = -0.39$, $t = -6.33$, $p < 0.001$). There were no significant interactions with the group.

### 3.3.3 LIs based on task-evoked activity in the Temporal Lobes

#### 3.3.3.1 Overt Sentence Reading

For the temporal lobe masks, a Bayesian independent samples t-test revealed a Bayes factor of 4.87, indicating moderate evidence in support of the null hypothesis. The chi-squared analysis gave the same result as the analysis of frontal lobes and verified that the groups did not differ regarding the number of typically or atypically lateralised individuals ($\chi^2 = 0.46$, $p = 0.50$). As above, the mean LIs indicate this is not a robustly lateralized task at the group level, though again the range of values indicates considerable variation among individuals (Fig. 3.3; Table 3.2).

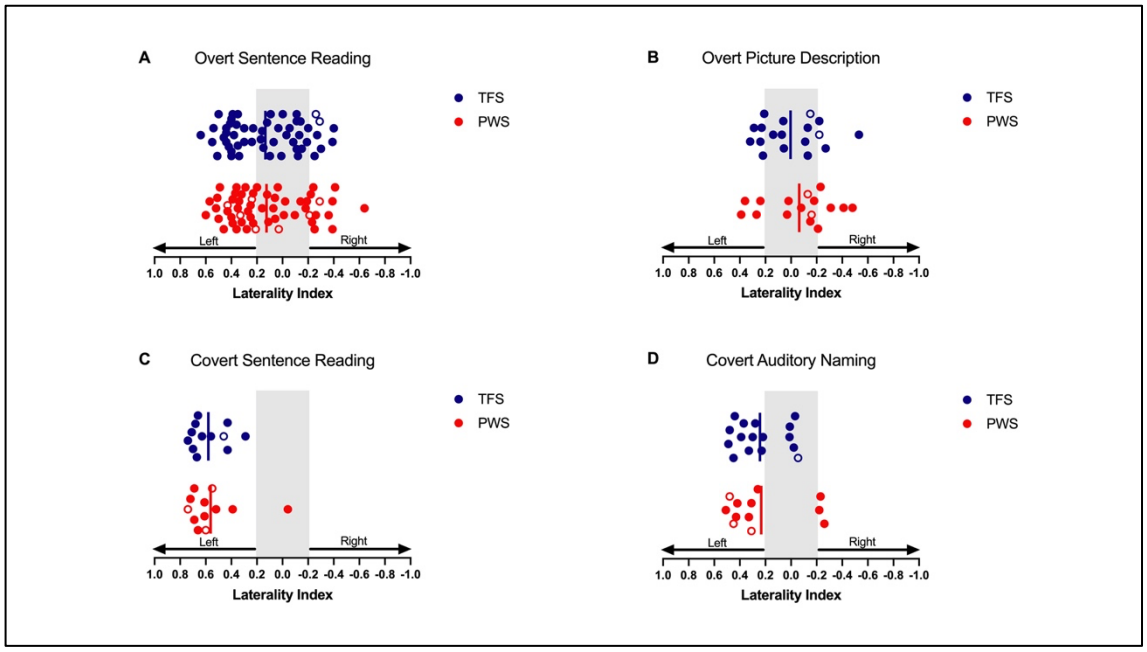



***Figure 3.3: Laterality indices in PWS and TFS based on activity in the temporal lobes*** *(see Fig3.2 for details). Results from the Bayesian independent samples t-tests indicated a BF in support of the null hypothesis of (A) 4.87 for overt sentence reading (PWS = 56, TFS = 53), (B) 2.36 for overt picture description (PWS = 16, TFS = 18), (C) 2.61 for covert sentence reading (PWS = 12, TFS = 12) and (D) 2.80 for covert auditory naming (PWS = 12, TFS = 16) tasks.*

#### 3.3.3.2 Overt Picture Description, Covert Sentence Reading, Covert Auditory Naming

For the temporal lobe masks, we examined LIs for the overt picture description task, covert sentence reading task, and covert auditory naming task (Fig. 3.3; Table 3.2). Bayesian independent samples t-tests found no support for the alternative hypothesis with Bayes factors of 2.36, 2.61, and 2.80, respectively, indicating anecdotal evidence in support of the null hypothesis. Furthermore, chi-squared analyses found the same results as for the frontal lobe analyses, which confirmed that the groups did not differ in terms of the number of typically or atypically lateralised individuals in the overt picture description task ($\chi^2 = 0.28$, $p = 0.9$), covert sentence reading task ($\chi^2 = 1.04$, $p = 0.30$) and covert auditory naming task ($\chi^2 = 0.13$, $p = 0.72$) (see Table 3.2).

#### 3.3.3.3 Laterality Effect of Different Tasks

The same linear mixed model analysis as above was performed on the data from the temporal lobe masks to test differences in lateralisation between covert and overt tasks (Fig. 3.3). Similarly to the above, the model revealed that the covert tasks (N = 51, LI = 0.40, *SE* = 0.04) showed

significantly more robust left lateralisation than overt tasks (N = 143, LI = 0.09, *SE* = 0.02) (β = -0.30, *t* = -4.32, *p* < 0.001).

### 3.3.4 Test-retest Reliability Scores

We compared the differences between these two matched measurements to analyse the tasks' reliability using intraclass correlation coefficient (ICC) analysis (Fig. 3.4). For the activity based on the frontal lobe ROI, test-retest reliability was found to be moderate for the overt sentence reading (ICC = 0.67), whereas it was revealed to be poor for the overt picture description task (ICC = 0.47). Regarding the temporal lobe ROI, test-retest reliability scores were moderate for both the overt sentence reading task (ICC = 0.73), and the overt picture description task (ICC = 0.73).

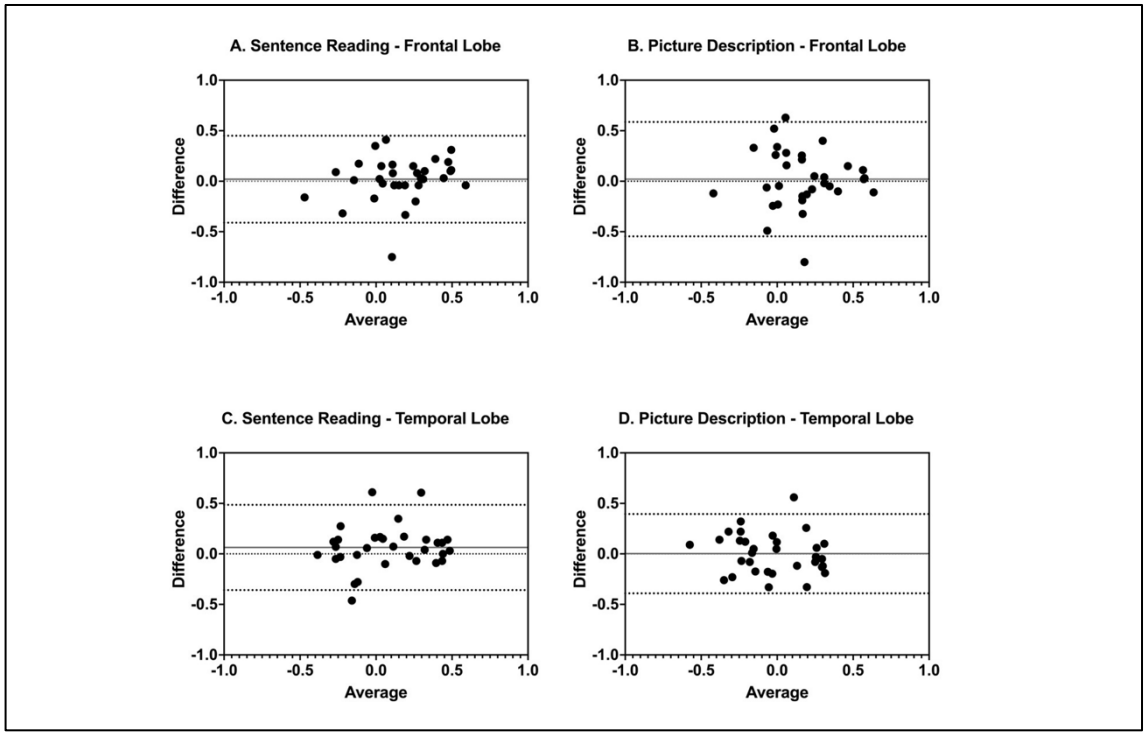



***Figure 3.04: The Bland Altman plots show the LI differences in matched tasks carried out at two different time points.*** *For each measurement of two tasks and two lobes (A, B, C, D), the x-axis represents the average LIs measured at these two different time points. The y-axis represents the difference in LIs between two measurement time points. The straight grey horizontal line in the middle is the mean of the differences, while the middle-dotted line corresponds to hypothetical zero differences. The gap between these two represents the bias. Upper and lower dotted horizontal lines indicate the limits of agreement (+1.96 x SD and -1.96 x SD).*

### 3.3.5 LIs for task-evoked activity in Pars Opercularis (BA44) and Pars Triangularis (BA45)

We analysed the LI values within more focal regions of interest, specifically the pars opercularis (BA44) and pars triangularis (BA45) of the inferior frontal gyrus (Table 3.2). This approach was adopted to facilitate a more detailed examination since these regions in the left hemisphere correspond to "Broca's Area" and are usually robustly activated by speech and language tasks. Again, we found similar results suggesting no differences between groups in LIs (see Supplementary Material). For BA44, data from the overt sentence reading task (which has the largest sample size) provided moderate evidence in favour of the null hypothesis with the Bayes Factor (BF) of 4.82. For the other tasks, we found only anecdotal evidence in favour of the null: overt picture description (BF = 2.69), covert sentence reading (BF = 2.24), and covert auditory naming (BF = 2.05). For BA45, we only found anecdotal evidence in favour of the null hypothesis for each of the four tasks; overt sentence reading (BF = 2.91), overt picture description (BF = 2.08), covert sentence reading (BF = 2.49) and covert auditory naming tasks (BF = 2.78).

Chi-squared analyses also revealed no significant differences between the groups in terms of the number of participants in each group who were typically or atypically lateralized: BA44 in overt sentence reading ($\chi^2 = 0.01$, $p = 0.93$), overt picture description ($\chi^2 = 0.03$, $p = 0.85$), covert sentence reading ($\chi^2 = 1.04$, $p = 0.30$), covert auditory naming ($\chi^2 = 012$, $p = 0.72$); BA45 in overt sentence reading ($\chi^2 = 0.20$, $p = 0.65$), overt picture description ($\chi^2 = 1.40$, $p = 0.23$), covert sentence reading ($\chi^2 = 0.38$, $p = 0.53$), and covert auditory naming task ($\chi^2 = 0.10$, $p = 0.75$) tasks (see Table 3.2).

## 3.4 Discussion

Since the pioneering findings of Paul Broca, it is well documented that most people rely more on their left hemisphere than their right to use language. In the current study, we investigated the theory as to whether PWS have reduced hemispheric specialisation compared with typically fluent speakers. We looked at data obtained across different language and speech tasks, namely overt sentence reading, overt picture description, covert sentence reading, and covert auditory naming

that we obtained in different functional MRI studies. Pooling data across these different versions allowed us to investigate one task (overt sentence reading) in a relatively large sample of 56 PWS compared with 53 TFS. We analysed LI-weighted means for task-evoked activity in frontal and temporal lobes and repeated the same analyses for portions of the inferior frontal gyrus involved in language processing, namely the pars opercularis (BA44) and pars triangularis (BA45) regions. We did not exclude stuttering epochs from the overt speaking data in this analysis since it is possible that stuttering evokes right hemisphere activity. The inclusion of stuttering epochs therefore made it more likely we would detect a rightwards pattern of lateralisation in people who stutter should one exist.

Our main findings are as follows: (1) there was no evidence in support of the idea that PWS are differently lateralized relative to people who are typically fluent and some anecdotal and moderate evidence in support of the idea that they are equally lateralized; (2) leftwards lateralization was most robustly observed for the covert tasks relative to the overt tasks and this effect was seen in both groups.

### 3.4.1 No Differences in Laterality between PWS and TFS

The idea that people who stutter are differently lateralized for language has a long history dating back to Samuel Orton (1927), who first proposed this idea, and it is a persistent "urban" myth believed by many individuals with lived experience of stuttering. The support for this myth comes from two main sources of information: (i) it has been suggested that left-handedness may be a risk factor for stuttering and that it occurs more frequently in PWS than in the general population (Howell, 2007; Papadatou-Pastou et al., 2023), which is often assumed to be associated with more rightward lateralization for language in the brain (Orton, 1927; Travis, 1978); (ii) some early observations and neuroimaging studies proposed atypical hemispheric activity during stuttered-speech that shifted to the left when individuals spoke fluently (Fox et al., 1996; Jones, 1966; Kell et al., 2018; Neumann et al., 2005).

First, our groups of people who stutter and typically fluent speakers did not differ in the distribution of left and right-handedness, while it is important to note that one of the studies with 38 participants (23 PWS, 15 TFS) recruited only right-handed male participants. Nevertheless, the distribution of handedness between our groups remained stable, even when data from that study were excluded from our handedness analysis. Therefore, our data is consistent with evidence indicating that stuttering is independent from handedness (Records et al., 1977; Salihović & Sinanović, 2000; Webster & Poulos, 1987). We find no support for the idea that PWS are more likely to be left-handed than typically fluent speakers, nor that their handedness alters the typical pattern of left-hemispheric cerebral dominance for speech and language.

In our main findings, we found that PWS and TFS show equivalent levels of language lateralization across a range of tasks. The means for groups of PWS and TFS were very similar, and they had very similar distributions of participants categorised as typically (left) or atypically (right or bilaterally) lateralised. This pattern of results was seen for our large region of interest analyses, where we compared task-evoked activity in the frontal and temporal lobes, as well as in our analyses of more focused regions of interest in the inferior frontal cortex. The results of our statistical analyses found no support for the idea that PWS are differently lateralized on average relative to people who are fluent speakers, in fact, in some cases we found moderate support for the hypothesis that they are not differently lateralized. These results are compatible with a magnetoencephalography (MEG) study which compared language lateralisation in preschool children who stutter and controls during picture naming tasks (Sowman et al., 2014). The authors reported that the language was mostly left lateralised in both groups over frontal, temporal and parietal regions without significant differences between groups.

The lack of a rightward lateralization during speech production in PWS might appear inconsistent with the robust finding of right hemisphere overactivity reported in several studies of PWS (Kell et al., 2009; Neef et al., 2018; Neumann et al., 2005; Watkins et al., 2008). This right hemisphere overactivity in the frontal operculum / anterior insula was described as one of the “neural signatures” of stuttering (Brown et al., 2005). In our frontal lobe analysis, both the frontal

operculum and the anterior insula were included in the mask, and the BA44 mask included at least a portion of the frontal operculum. Any overactivity in these areas would have contributed to the data being compared between the two hemispheres in the calculation of laterality indices. The apparent discrepancy in these findings is explained by two key features of the laterality calculations. First, voxel values between the two hemispheres were compared across a range of statistical thresholds, so that even subthreshold (in a whole-brain group comparison) data from both hemispheres contributed to the overall calculation. Second, activity was summed for supra-threshold voxels over large regions (whole lobes in the first instance) rather than specific portions of gyri identified as unilaterally overactive in PWS. In this latter case, high voxel values in focal locations, such as the right anterior insula, could have been offset by similar voxel values distributed more widely across different portions of left frontal lobe when sampled across the whole region.

Another apparent discrepancy with our findings comes from reports that therapeutic interventions for stuttering demonstrate the potential to enhance neural activity within the left hemisphere of the brain (Toyomura et al., 2015) or shift the balance of activity from the right hemisphere to the left during speech production (Kell et al., 2009; Neumann et al., 2005). However, neither of these previous studies statistically compared the activity between two hemispheres in PWS and controls. Focal areas of overactivation in one hemisphere during speech tasks in PWS might reflect a range of functions unrelated to language, such as inhibition, compensation or error responses (e.g., see: Neef et al., 2018). Furthermore, as explained above, the unilateral overactivity may be due to statistical thresholding, leading to the conclusion that there is no activity in one hemisphere because it is only visible sub-threshold and emphasizing the need for statistical comparisons between hemispheres.

To our knowledge, there is only one study that found support for the idea that PWS are differently lateralized for language, which also investigated language laterality directly. Using near-infrared spectroscopy, Sato et al. (2011) reported laterality during passive listening of syllable pairs, which included either a phonemic contrast (e.g., /itta/ vs. /itte/) or prosodic contrast (e.g., /itta/ vs. /itta?/)

(Sato et al., 2011). Specifically, adults, school-aged children and pre-school children who stutter did not show the expected leftward lateralisation for processing the phonemic contrast, whereas controls showed a pattern of leftward and rightward lateralisation for phonemic and prosodic contrasts, respectively (Sato et al., 2011). Although the results of a direct comparison of language laterality between PWS and controls differ from our findings, it must be considered that this study involved passive listening to words rather than production.

Studies on structural hemispheric differences in PWS can offer valuable insights for interpreting functional activity. For instance, some earlier structural imaging studies in PWS reported lower leftward (or more rightward) asymmetry in the planum temporale, which was correlated with stuttering severity (Foundas et al., 2004). However, analysis of planum temporale asymmetry with a large population overlapping with the participants reported here found no differences between PWS and TFS and also no relationship with handedness (Gough et al., 2018).

### 3.4.2 LIs are More Strongly Left Lateralised for the Covert Tasks

In our findings, covert language tasks were significantly more lateralised compared with overt tasks. This finding is consistent with another fMRI study that reported more robust language lateralisation for covert language tasks than overt ones (Partovi et al., 2012). The reason may be that the cortical motor areas that send hundreds of commands to dozens of muscles bilaterally during overt speech production are not involved in covert speech. When the motor cortex is heavily involved in overt articulation, perhaps this bilateral pattern of task-related activity reduces laterality measured by methods that include these areas. As seen in our overt tasks (see Fig. 3.1), pre- and post-central gyri are reliably activated bilaterally during overt speaking tasks compared with a passive baseline task (meta-analysis from PET and fMRI studies: Turkeltaub et al., 2002). It is worth noting, however, that the analysis of the activity in BA44 and BA45 regions of interest, that do not include data from the pre- and post-central gyri, also show stronger lateralization for the covert than the overt tasks (see Supplementary Material).

Another possible reason for stronger laterality during covert tasks in our findings needs to be highlighted. Both tasks (covert sentence reading and auditory naming) involved continuous data acquisition during imaging. In contrast, the overt speech production tasks were carried out using sparse sampling to allow participants to hear themselves during the task and to avoid potential head movement artefacts due to speech production during acquisition of the imaging data. Sparse sampling is feasible because the haemodynamic response is slow, only peaking some 4-6 seconds after the event, hence speech production can occur during a relatively long window of silence (6-10 s across different studies) before the measurement that takes 2-3 s occurs (Hall et al., 1999). Sparse-sampling functional MRI is the most effective way of reducing motion-related noise in the images due to overt speech production. Furthermore, sparse-sampling acquisitions are demonstrably better than continuous imaging for detecting auditory responses in temporal lobe cortex (Blackman & Hall, 2011; Gaab et al., 2007). However, to match the power of continuous imaging using simple block designs, sparse-sampling acquisitions need to be longer (Nebel et al., 2005). They are also less sensitive to variations in the haemodynamic response within individuals and between them. Variations in task design (event vs. block designs), timing (short or long delays in measurement), and in analysis methods (convolution with the haemodynamic response function vs. finite impulse response models) hamper direct comparisons of the sensitivity of sparse-sampling relative to continuous acquisitions (Perrachione et al., 2011). It remains unclear, however, why laterality should differ between sparse-sampled and continuous acquisition since all factors affecting the sensitivity of the measurement should affect both hemispheres equally. Nevertheless, with our current datasets, we cannot disentangle possible causes of our finding that covert tasks were more strongly lateralized than overt ones since this factor is confounded with the measurement difference.

## 3.5 Limitations

Laterality indices allow us to compare the activity of thousands of voxels between two hemispheres in a single metric; however, useful information may be lost with this approach. LI scores deriving from fMRI results are limited in temporal resolution, which is not informative for

possible differences in lateralisation milliseconds before the speech starts. For example, Neef and colleagues (2015) used transcranial magnetic stimulation during a verb generation task to record motor-evoked potentials from the tongue (Neef et al., 2015). They reported atypical cortical excitability patterns between left and right tongue motor cortical areas in adults who stutter milliseconds before speech onset. The current fMRI study would not be able to detect these dynamic differences in cortical excitability because of the relatively slow signal of the haemodynamic response (Glover, 2011).

It is also worth noting that even though test-retest reliability was found to be moderate for the temporal lobes during sentence reading and overt picture description task, it was poor for frontal lobe measurements during picture description and moderate for sentence reading. Similarly, Jansen and colleagues (2006) reported low test-retest scores within Broca's area for a synonym decision task involving accessing semantic concepts; however, the reliability was higher for the temporoparietal regions. Another limitation of the study is that we could not test reliability for the covert tasks since these data were acquired only once in each participant.

In comparing activity between hemispheres, choices need to be made regarding the regions of interest. The advantage of large regions of interest, such as whole hemispheres or lobes, is that spatial variation in language processing among participants will be captured. The disadvantage of large regions is that many of the voxels included do not show task-evoked activity. ROI selections were made relying on masks of the frontal and temporal lobes, as these encompass the areas where language tasks usually elicit activity. In addition, we quantified the LI values within more focal regions of interest, specifically the pars opercularis (BA44) and pars triangularis (BA45) situated within the inferior frontal gyrus, thereby affording a finer-grained examination.

## 3.6 Conclusions

Previous fMRI findings consistently reported an overactive right hemisphere in stuttering during speech tasks but did not statistically compare the functional activity between hemispheres. Therefore, they do not provide direct evidence for altered hemispheric specialisation in people

who stutter during language production. Here, our results close that gap by statistically comparing the functions of two hemispheres to test the altered hemispheric specialisation theory with a threshold-independent laterality analysis. Our findings indicated no difference in the hemispheric specialisation in frontal and temporal regions of PWS compared with typically fluent speakers while performing four different speech and language tasks. We also reported that covert tasks were substantially more lateralised than overt tasks for both groups. These data were obtained using continuous imaging, whereas the overt tasks were carried out using sparse sampling. Therefore, task choice and data acquisition may be important factors to consider when measuring laterality.

# 4

# The effects of theta-gamma peak stimulation on sensorimotor learning during speech production


## Abstract

Transcranial alternating current stimulation (tACS) is a non-invasive neuromodulatory tool that is thought to entrain intrinsic neural oscillations by supplying low electric currents over the scalp. Recent work has demonstrated the efficacy of theta-gamma phase-amplitude coupled tACS over primary motor cortex to enhance motor skill acquisition and motor recovery after stroke. Here, we wished to assess the efficacy of tACS delivered with 75-Hz gamma coupled to the peak of a 6-Hz theta envelope (theta-gamma peak; TGP) at an intensity of 2 mA peak-to-peak to enhance sensorimotor learning during speech production. Sensorimotor learning was measured by shifting the formant frequency of vowels in real-time as speech is produced and measuring the adaptation to this altered feedback. The study was a between-subjects, single-blind, sham-controlled design. We hypothesised that participants who perform the speech task while receiving TGP tACS over the speech motor cortex (n = 30) would show greater adaptation to altered auditory feedback than those receiving sham stimulation (n = 30). Contrary to this hypothesis, there was no effect of TGP tACS on adaption to the upwards F1 shift in auditory feedback in either the final 30 trials of the learning phase or in the first 15 trials of the after-effect phase. However, in an exploratory analysis of all 90 trials in the after-effect phase, the mean F1 value for the TGP tACS group was significantly lower than that for the sham group, suggesting that TGP tACS administration during a speech adaptation task may enhance the retention of the adapted state. This outcome aligns with previous tACS studies, which have shown an improvement in the persistence of motor learning, and it uniquely suggests that theta-gamma coupling could be a significant factor in maintaining motor learning in speech for an extended period. Nonetheless, these findings are preliminary and

highlight the need for further research to validate these results and to deepen our understanding of the effects of TGP tACS on speech motor learning.

## 4.1 Introduction

Non-invasive brain stimulation methods have provided promising results in enhancing the acquisition of novel motor skills and efficacy of rehabilitative interventions. Several studies demonstrated the effectiveness of transcranial direct current stimulation (tDCS) to enhance the rate and retention of learning (Reis et al., 2009). TDCS can improve upper limb use following stroke when used in conjunction with therapy (Allman et al., 2016). Similarly in the speech domain, it can aid speech therapy in post-stroke aphasia (Marangolo et al., 2013) and enhance fluency in people who stutter (Chesters et al., 2018; Moein et al., 2022). Recently, another form of brain stimulation, namely transcranial alternating current stimulation (tACS) has also been shown to be effective (see a systematic review and meta-analysis: Hu et al., 2022). Specifically engaging dynamic activity linked to learning is a promising approach (Akkad et al., 2021; Rustamov et al., 2022), and indeed early data suggest that a specific form of tACS, gamma coupled to the peak of a theta envelope (theta-gamma peak; TGP) may increase learning with a larger effect size than seen in similar studies using tDCS (Akkad et al., 2021). To our knowledge, TGP tACS has not been used to improve sensorimotor learning in the speech motor domain. Therefore, the primary objective of the proposed study was to assess the efficacy of TGP tACS in enhancing sensorimotor learning in speech by using a sensorimotor adaptation task in young healthy controls. Positive evidence for the efficacy of TGP tACS in enhancing learning in the speech motor domain would indicate that it could be an effective form of stimulation when used in conjunction with speech fluency training in people who stutter and to support other rehabilitation efforts which focus on speech production.

The task selected for this study involves sensorimotor learning in speech using an adaptation paradigm in which the auditory feedback of participants' speech production is altered in real-time, leading participants to adjust their speech production in response to compensate for this change. (Houde & Jordan, 1998; Lametti et al., 2018; Niziolek & Guenther, 2013; Tang et al., 2021). This form of adaptation investigates the processes that govern how we acquire speech motor patterns by integrating sensory feedback with production. Several previous studies employed speech or

pitch adaptation tasks to investigate whether brain stimulation can enhance sensorimotor learning in fluent speakers (Deroche et al., 2017; Lametti et al., 2018; Li et al., 2023; Scott et al., 2020; Shum et al., 2011). Such tasks are a good choice for these investigations as it is possible to show gains in learning. In contrast, many other speech and language tasks show ceiling effects in young typically fluent speakers, which limit the possibility to show positive effects of brain stimulation (e.g., Wiltshire & Watkins, 2020).

Speech adaptation tasks alter feedback by shifting the formant frequencies that characterise vowel identity during the steady-state portion of syllable production (Houde & Jordan, 1998). The acoustic spectrum of a speech syllable contains several formants representing acoustic energy around a particular frequency corresponding to specific resonances in the vocal tract. Vowels are characterised by the first two formants (F1 and F2). When the frequency of the formants is shifted, the speaker compensates by altering speech production (Purcell & Munhall, 2006). For example, when speakers utter a word such as “head” and the frequency of F1 is decreased or increased, they may perceive their production as sounding closer to the vowel sounds contained in words like “had” or “hid”. To achieve production closer to the intended vowel, the speaker compensates by adjusting the formant frequencies in their speech production in the direction opposite to the shift applied to feedback. Speakers are rarely aware of the frequency shift applied to the feedback, and their adaptive speech responses are not affected by explicit cognitive strategies (Munhall et al., 2009). The neural correlates of speech motor adaptation involved in executing articulatory commands, predicting their sensory consequences, and integrating sensory feedback for adapting subsequent movements likely involves ventral premotor and primary motor cortex, the cerebellum along together with inferior parietal and superior temporal regions (Segawa et al., 2015; Tourville et al., 2008; Parrell et al., 2017).

Recently, the speech adaptation task has been used in conjunction with non-invasive brain stimulation to investigate the causal contribution of these brain regions to this form of sensorimotor learning (Lametti et al., 2018; Scott et al., 2020; Shum et al., 2011; Tang et al., 2021). One study used anodal transcranial direct current stimulation (tDCS) to increase cortical

excitability of the representations of the speech articulators in left primary motor cortex (M1) and of the right posterior lobe of the cerebellum during speech motor adaptation (Lametti et al., 2018). During speech production, participants heard their feedback in real-time with an increase in F1 frequency. Relative to a group who did not receive any stimulation (sham control), the group who received anodal tDCS over the cerebellum compensated for the altered feedback by decreasing the frequency of F1 to a greater extent; they did not change the frequency of F2. In contrast, the group who received anodal tDCS over M1 compensated for the altered feedback by decreasing F1 and increasing F2 to a significantly greater extent than the sham control group. These results were interpreted as indications of different roles for the cerebellum and M1 in sensorimotor learning. Specifically, it was suggested that the cerebellum involves compensating for the acoustical error (shift in F1 frequency) alone, and M1 generates more global adaptation in response to altered auditory feedback by moving production towards that of a target vowel rather than simply offsetting the acoustical error in the feedback (Lametti et al., 2018).

The current study expands on this previous work by exploring the efficacy of another kind of non-invasive brain stimulation, namely transcranial alternating current stimulation (tACS), to facilitate the sensorimotor learning of speech. TACS supplies low currents across the brain that result in weak modulation of membrane voltage in a temporally coordinated manner (for a review; Antal et al., 2013). The sinusoidal currents delivered during tACS are thought to mimic and perhaps promote intrinsic neural oscillations when delivered in a physiologically relevant manner. This entrainment of neural oscillations can provide efficient communication between neural networks so that presynaptic inputs are synchronised to arrive during moments of low inhibition thereby promoting the likelihood of action potentials occurring in the postsynaptic network (Fries, 2005, 2015). This modulation is analogous to pushing a swinging pendulum at the right time to be able to intervene more efficiently and may be adequate to entrain neurons at the tACS frequency. Previous work showed that tACS improved motor skill learning, increased the magnitude of vocal compensation, reduced symptoms of Parkinson's disease, and improved phonological processing

and reading accuracy in dyslexia (Akkad et al., 2021; Li et al. 2022; Guerra et al., 2020; Marchesotti et al., 2020; Schilberg et al., 2018).

The efficacy of tACS is thought to be enhanced by coupling the frequency of the stimulating current with the frequency of intrinsic neuronal oscillations. In hippocampal-dependent skill learning, gamma activity at 75 Hz coupled to the peak of slower, theta activity (6 Hz) is common (Bragin et al., 1995; Colgin, 2015; Lasztóczi & Klausberger, 2014). For instance, Lopes-dos-Santos and colleagues (2018) found that during memory encoding, 60-80 Hz activity, which increases significantly, is coupled to the peak of the underlying theta oscillation. This suggests that the precise relationship between gamma activity and theta phase may be crucial for its function. In M1, gamma activity, particularly that at approximately 75-Hz, is pro-kinetic, being increased during actual rather than imagined movement (see Nowak et al., 2018 for review) and substantially enhanced in patients with dyskinesias (Swann et al., 2018). Similar to hippocampal-dependent learning, gamma coupled to the peak of a theta envelope appears to be important in M1-dependent learning: tACS consisting of a 75-Hz sinusoid present during the peak of a 6-Hz theta envelope delivered over M1 was demonstrated to increase motor skill acquisition in a thumb abduction task in healthy adults compared with sham and gamma coupled to the trough of a theta envelope (Akkad et al., 2021). Furthermore, motor recovery after stroke was recently linked to an increase in M1 theta-gamma phase-amplitude coupling (Rustamov et al., 2022).

In the current study, we hypothesised that people who perform the speech task with altered auditory feedback while receiving TGP stimulation over the speech motor cortex in left M1 would show greater compensatory responses to altered auditory feedback compared with those receiving sham tACS. We increased the frequency of the F1 feedback and investigated the magnitude of expected decreases in F1 and increases in F2 produced in response. The directions of these changes in response to increased F1 frequency feedback was based on those described in previous work (Lametti et al., 2018; MacDonald et al., 2011; Tang et al., 2021).

## 4.2 Methods

### 4.2.1 Participants

We recruited healthy people who were 18-50 years old, able to give informed consent, and grew up speaking English. We excluded people with impaired hearing, a history or current diagnosis of dyslexia or other language or speech disorder since weaker magnitudes of compensatory responses to altered auditory feedback have been shown in children with dyslexia (van den Bunt et al., 2018) and in a group of people who stutter (Cai et al., 2012).

This research expands on a previously reported finding that tDCS improves sensorimotor learning in speech following an increase in F1 feedback (Lametti et al., 2018). In this previous study, 20 participants received 2 mA anodal tDCS over the ventral motor cortex corresponding to the representations of speech articulators and 20 received sham tDCS. Participants who received active tDCS significantly reduced their F1 and increased their F2 production during the learning phase to a greater extent that the reductions seen in the group who received sham stimulation. An effect size (Cohen's d) of 0.65 was reported for the group difference in F1 reduction, averaged across the learning and after-effect stages of the experiment (note the after-effect stage involves removal of the altered feedback and did not show a significant group difference, so this may be a conservative effect size). For the current study, a power calculation (G power 3.1), indicated that 30 participants in each group should be sufficient to detect the same sized group difference in reduction in F1 in response to an upwards shift in F1 feedback, significant at 5% (one-tailed) with 80% power. It is worth noting that compared with sham stimulation, TGP tACS over the hand representation in M1 (Akkad et al., 2021) during a thumb abduction task resulted in 26% greater acceleration gain from baseline in motor learning, which was a large effect (Cohen's d = 0.98).

### 4.2.2 Procedure

The study used a between-subjects, single-blind, sham-controlled design. In the beginning of each session, the same instructions were read to each participant. Participants engaged in a speech production task requiring them to read aloud words presented on a computer screen. Speech was

recorded via a head-mounted microphone (Shure WH20) placed 4 - 7 cm away from the participant's right corner of the mouth. Each word was presented for 1500 ms on the computer screen independently, and the inter-trial-interval will be set at 750 ms. Words appeared in a pseudorandom order, an equal number of times. After each utterance, participants heard their voice over headphones (Sennheiser HD 380 pro) with an imperceptible delay (27 ms) (Kim et al., 2020). MATLAB Mex-based program Audapter (with MOTU Microbook IIc external soundcard) was used to alter the auditory feedback of speech equal to 110 mel (Tang et al., 2021). During the phase when the altered auditory feedback was applied, participants were predicted to compensate for the mismatch between the expected auditory target and altered auditory feedback by reducing the F1 frequency. Based on previous work, we also expected participants to increase the F2 frequency of their speech production (Lametti et al., 2018; Tang et al., 2021). This adaptation is also typically present in the initial few trials during the after-effect phase when auditory feedback returns to normal.

The stimulating electrodes were attached to the head before the start of the experiment. The experiment included four phases depicted in Fig. 4.1.A: vowel exploration, baseline, learning and after-effect. The first phase allowed participants to explore vowel space when they produced "dead", "bed", "head", "dad", "bad", "had", "did", "bid", "hid" 15 times for each with normal feedback. The rationale of this phase was to record the formant frequencies used for F1 and F2 productions of these previously learned words for each participant, which then allowed us to compare the possible frequency adjustments towards these words in response to altered auditory feedback. After the vowel exploration phase, the stimulator was turned on and there was a short break during which we confirmed that the participant was comfortable and ready to proceed. The baseline phase started and participants produced the words "head", "bed", and "dead" 15 times each, containing the same vowel /ɛ/, with normal feedback, which gave a measure of production with stimulation before learning started. In the learning phase, participants produced "head", "bed", and "dead" 75 times each with altered auditory feedback. Finally, participants produced "head", "bed", and "dead" 30 times each again with normal feedback in the after-effect phase,

which gave a measure of the maintenance of sensorimotor learning in speech. There were 30-sec breaks after every 45 utterances. TACS was delivered approximately for 20 mins starting during the baseline phase and continuing during the learning and after-effect phases.

### 4.2.3. tACS

The somatotopy of the representations of the speech articulators along the precentral gyrus is such that a dorsal laryngeal representation is found ventral to the hand representation, followed by representations of the lip and tongue moving ventrally and anteriorly along the gyrus, with a ventral laryngeal representation located on the subcentral gyrus (Eichert et al., 2020). We delivered stimulation over the ventral two-thirds of the precentral gyrus to target these speech articulators as shown in Fig. 4.1B. One electrode (5 x 5cm) was placed on the left side of the head, with the top right (posterior) corner of the electrode positioned at a point one-third of the length along a line connecting the vertex to the tragus (Lametti et al., 2018) and the other electrode was placed over the posterior midline (Pz). We used Pz instead of the orbitofrontal cortex to avoid visual disturbances that can arise from tACS near the eyes. With this montage setup, the distribution of the current flow was simulated using SimNIBS software which is shown in the Fig. 4.1C. We have confidence that the motor representations of the speech articulators are encompassed by this large electrode, regardless of the size of the head. Therefore, the electrode's size is advantageous in addressing the variation between individuals in the precise locations of these representations, as it ensures that they are adequately covered. We used horizontally held bandages that did not interfere jaw movements.

Participants were randomised to receive either tACS or sham stimulation and these assignments were concealed from participants. A person not involved in data collection generated a randomisation code for participants using a block size of four to ensure a close balance of participants allocated to each stimulation group throughout the study. Groups were balanced for gender. Note that our intention was that assignment of participants to receive tACS or sham stimulation was concealed from researchers involved in delivering the stimulation and analysing the data (i.e. that the study was "double-blind"). The visibility on the computer monitor of the

theta-gamma waveform meant that this was not possible for 22 participants, in whom we consider data collection to have been conducted in a “single-blind” manner. This is a deviation from our original pre-registration protocol. Based on the chi-square test (chi-squared = 2.08, p = 0.149), there was no significant association between group assignment and correct responses to the stimulation condition, indicating successful blinding, with 15 out of 31 participants in the sham group and 20 out of 30 participants in the TGP tACS group correctly reporting the stimulation protocol. The researcher was blinded to the group allocation during data analysis, however, as planned.

The active stimulation condition included gamma frequency stimulation at 75-Hz delivered during the peak of a 6-Hz theta envelope at an intensity of 2 mA peak-to-peak as depicted in Fig 4.1D (Akkad et al., 2021). Unlike the active stimulation condition in which the entire theta-gamma peak amplitude coupled waveform was delivered, the sham stimulation condition only included the delivery of the beginning of the waveform, specifically 10 seconds of continuous sinusoidal 6-Hz stimulation. In this way, participants only felt the initial sensation of stimulation at the start of the waveform, which is a similar sensation to the active condition without causing any further neural modulation. Therefore, this protocol was thought to be sufficient to conceal the stimulation condition from the participant. Once the session ended, the participants completed a treatment identification questionnaire to assess the effectiveness of the stimulation condition concealment protocol as well as a questionnaire on possible side effects.

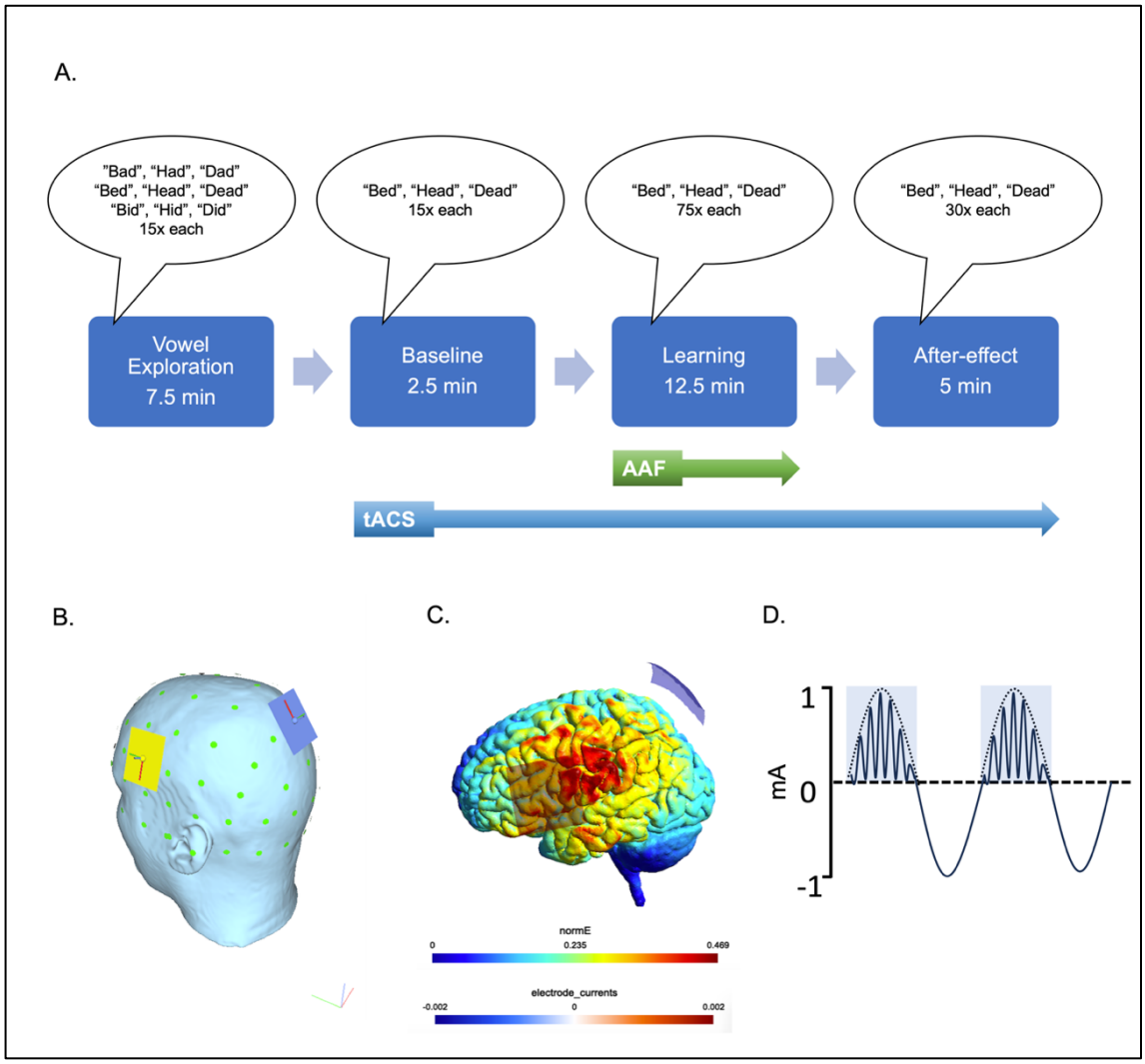



***Figure 4.01: (A) Schema depicts the experimental design with four phases: vowel exploration, baseline, learning, and after-effect.*** *Participants read one-syllable words from a computer screen. tACS was delivered during the baseline, learning phases, and after-effect phases. The total time of the experiment lasted approximately 1-hour. tACS: transcranial alternating current stimulation; AAF: altered auditory feedback. (B) One electrode (5 x 5cm) was centred over the ventral motor cortex (yellow, approximately FC5; see text for details on positioning) to target the speech articulators. The other electrode was centred over the posterior midline (blue, Pz). (C) Current flow simulation: estimated distribution of the current flow acquired at current peaks. NormE bar represents the strength of the electric field. Electrode_currents bar depicts the amplitude of the electric current, 2 mA for the anode electrode; -2 mA for the cathode electrode. (D) tACS waveform: gamma frequency stimulation was delivered during the peak of a theta envelope.*

### 4.2.4 Analysis of data

MATLAB (Mathworks) and the software package Praat (Boersma & Weenink, 2001) were used to analyse speech acoustics. Speech was recorded at 16000 Hz using custom MATLAB scripts. The centre of each vowel was detected through a visual examination of the speech waveform in MATLAB. Finally, we used Praat to perform linear predictive coding (LPC) to measure each vowel's average F1 and F2 values over a 25 ms (400 samples) segment at the centre of each

vowel. LPC orders were chosen per subject to minimise variability in the extracted formants. We removed datapoints that were errors (wrong word repeated, coughs, no or incomplete responses) and where the estimated formant frequencies exceeded 3 SDs of the mean for that phase of the experiment for each individual. All data were checked for normality using the Shapiro-Wilk test. We planned to transform data that was not normally distributed.

Our statistical analysis plan was based on that of Lametti et al., (2018). We first demonstrated that our two groups produced acoustically similar speech at baseline. The mean baseline frequencies for F1 and F2 (in Mel) were compared between the two groups using t-tests (two-tailed, uncorrected to avoid a false negative). We did not expect a significant difference between groups in either measure. In case of a difference in measures between the groups at the onset, any individuals in either group who exhibit outlier frequencies in F1 or F2 at baseline (defined as >3SDs from the mean) would be substituted, before the unblinding.

Sensorimotor learning for each participant was calculated by the mean change from baseline in F1 and F2 frequencies separately at the end of the learning phase (last 30 trials) and at the start of the after-effect phase (first 15 trials). These changes (learning) were assessed within each group separately using directional one-tailed t-tests against no change (i.e., zero; reduced F1 and increased F2 frequencies were expected, $p < .05$).

Our main hypothesis is that we expected a significantly greater magnitude of adaptation in F1 in the TGP tACS group relative to the sham group as previously seen using tDCS over M1. This was tested separately for the end of learning and initial after-effect trials with directional t-tests ($p < .05$). It is worth noting that the previous study (Lametti et al., 2018) found a significant group difference only for the trials at the end of learning and the difference in the initial after-effect trials was not significant though the pattern of results was similar.

We also tested for group differences in the magnitude of adaptation in F2 in the end of learning and initial after-effect trials respectively. We used non-directional t-tests ($p < .05$) since there was no significant difference between the groups receiving tDCS over M1 and the sham group in the

magnitude of adaptation in F2 in the previous study at either phase of the experiment (Lametti et al., 2018).

Previous work showed that participants who experienced an increase in F1 frequency during feedback produced combined changes in F1 and F2 that resulted in moving speech production closer to a target vowel in vowel space (Lametti et al., 2018; Tang et al., 2021). We also tested whether the magnitude of this combined change differed between groups in the current study. For each individual, we calculated the Euclidean distance in F1-F2 vowel space between the productions of "head", "bed", and "dead" during the last 30 trials of the learning phase and the first 15 trials of the after-effect phase and productions of "hid", "bid", and "did" during the vowel exploration phase (Lametti et al., 2018). The magnitude of the combined F1-F2 change was compared between groups using a non-directional t-test ($p < 0.05$) as there was no difference between the M1-tDCS and sham groups in the previous study in the learning and after-effect phases of the study.

## 4.3 Results

Data were obtained in 62 participants (31 in each group). One man was excluded from the sham group due to stuttering during the task and subsequently reporting a history of childhood stuttering. Due to a technical error, data from the after-effect block were lost for a woman in the TGP tACS group. The TGP tACS group comprised 30 participants (15 women) with data from 29 available for the after-effect phase, and the sham group comprised 31 participants (16 women). The groups were also matched for age (Table 4.1). Formant values exceeding three SDs from the mean F1 or F2 value for each participant in each block were removed (~0.02% of the data). Analysis revealed that the groups produced acoustically similar speech at baseline were matched for F1 and F2 frequency (F1: $t(59) = -0.96$, $p = 0.34$; two-tailed, uncorrected; F2: $t(59) = 1.70$, $p = 0.09$) (see Table 4.1).

| | **TGP tACS** | **Sham tACS** |
|---|---|---|
| Age (years) | 23.4 ± 4.9 | 23.7 ± 6.7 |
| Baseline F1 Trials 1-45 | 747 ± 86.8 | 767 ± 73 |
| Baseline F2 Trials 1-45 | 1468 ± 105.5 | 1427 ± 81.6 |
| Learning F1 Trials 241-270 | 713 ± 81.3 | 736 ± 71.7 |
| Learning F2 Trials 241-270 | 1480 ± 100.7 | 1433 ± 85.2 |
| After-Effect F1 Trials 271-285 | 720 ± 81.3 | 750 ± 68.8 |
| After-Effect F2 Trials 271-285 | 1478 ± 103.5 | 1435 ± 82.8 |

***Table 4.01: Illustration of the group details in terms of means and standard deviations (SD).*** *All the trial results were reported in Mel. TGP tACS: theta-gamma peak transcranial alternating current stimulation.*

### 4.3.1 Changes in F1 production

Fig. 4.2A shows the change in produced F1 frequency during the learning phase (trials 46-270; shaded region) and the after-effect phase (trials 271-360), compared with the baseline F1 values (trials 1-45). As expected, by the end of the learning phase, both groups showed a significant decrease in F1 frequency from baseline in response to an upwards shift in F1 feedback. The magnitude of adaptation in the TGP tACS group was 31% (one-sample t-test against zero, $t(29) = -6.65$, $p < 0.001$, one-tailed); and for the sham group was 27% (one-sample t-test against zero, $t(30) = -5.90$, $p < 0.001$, one tailed; Fig. 4.2B). This adaptive response in F1 was still evident in the first 15 utterances in the after-effect phase in both groups (TGP tACS group $t(28) = -5.82$, $p < 0.001$; sham group $t(30) = -4.37$, $p < 0.001$).

To test our hypothesis that TGP tACS would lead to significantly greater adaptation in F1 than sham stimulation, the means for the two groups at the end of the learning phase and the beginning of the after-effect phase were compared using directional two-sample t-tests. The amount of adaptation in each group did not differ for either phase (end of learning: directional $t(59) = -0.5$,

p = 0.31, Cohen's d = -0.13; start of after-effect: t(58) = -1.61, p = 0.06, Cohen's d = -0.42). In sum, TGP tACS has no effect on the magnitude of F1 adaptive changes in response to an F1 feedback perturbation during the learning phase.

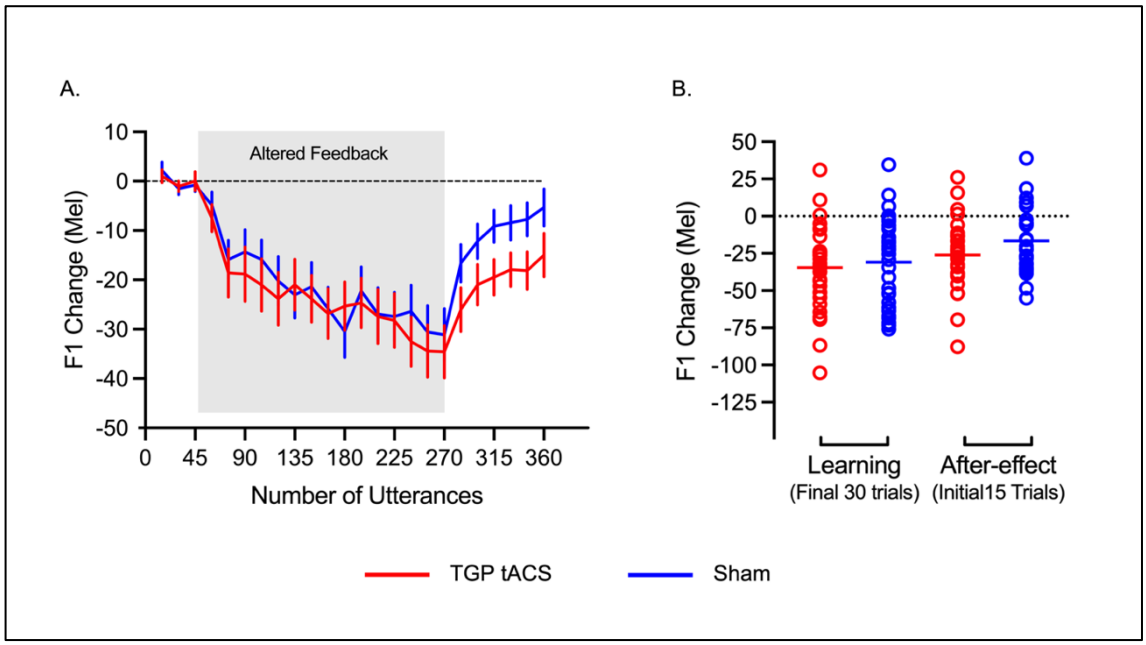



***Figure 4.02: Changes in production of F1 due to sensorimotor learning.*** *(A) Changes in F1 production in response to increased F1 feedback are shown for baseline, learning, and after-effect phases (note altered feedback was applied only during the learning phase, shaded area). Each datapoint represents the mean F1 frequency for 15 utterances with error bars indicating the standard error of the mean. A dashed line indicates the mean of the baseline trials. (B) The average changes in F1 frequency for the final 30 trials of the learning phase (trials 241-270) and the initial 15 trials of the after-effect phase (trials 271-285). Solid lines show the means for each group, the open circles indicate individual participant data. Red indicates TGP tACS group data and blue data from the sham group. TGP tACS: Theta-gamma-peak transcranial alternating current stimulation.*

### 4.3.2 Changes in F2 production

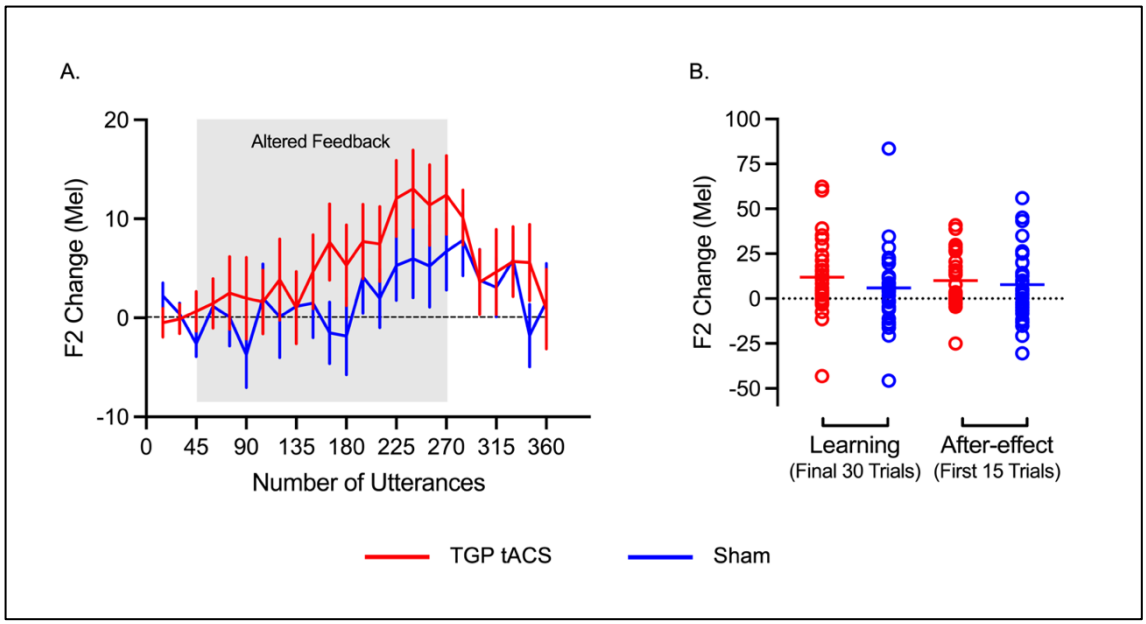



***Figure 4.03: Changes in F2 production due to sensorimotor learning.*** *(A) Changes in F2 frequency throughout the baseline, learning, and after-effect phases. (B) Average changes in F2 across the last 30 trials of the learning phase (trials 241–270) and initial 15 trials of the after-effect phase (trials 271 - 285). Refer to the legend in Fig. 4.2 for further information.*

Previous studies reported an increase in F2 frequency during vowel production in response to an upwards shift in F1 in the auditory feedback (Lametti et al., 2018); the magnitude of this shift is typically smaller and less consistently observed among individuals and studies (Lametti et al., 2018; Tang et al., 2021). Based on previous work (Lametti et al., 2018), we did not expect TGP tACS to modulate the size of the adaptation in F2 relative to sham. Figure 4.3A shows the change in produced F2 frequency from baseline, through the learning when the F1 upwards shift was applied to feedback and during the after-effect phase when normal feedback was restored.

Figure 4.3B shows the average changes in F2 from baseline for each group. By the end of the learning phase, the TGP tACS group adapted F2 by approximately 11% in response to the introduced 110 Mel shift in F1 frequency, whereas the adaptation in the sham group was around half of that, at 5%. A Shapiro-Wilk test indicated that the data for the magnitude of the F2 shift at the end of the learning phase significantly deviated from a normal distribution in both the TGP tACS group ($W = 0.92$, $p = 0.04$) and the sham group ($W = 0.88$, $p = 0.003$). For the after-effect phase, only the data in the TGP tACS group was not normal ($W = 0.92$, $p = 0.045$); while the

sham tACS group was normal (W = 0.97, p = 0.68). Additionally, an outlier was identified in the sham group with a value of 83.59 (Figure 3B), which is more than 3 SD above the group mean (M = 5.94, SD = 21.39). Rather than transform the data as planned, we used the Wilcoxon signed-rank test to compare the change against baseline and non-parametric Mann-Whitney U test to compare the groups, which showed a significant change in F2 from baseline for the TGP tACS group (V = 373, p < 0.001, r = 0.71) and the sham group (V = 334, p = 0.047, r = 0.35), with a stronger effect in the TGP tACS group. To compare the adaptation between groups, Mann-Whitney U tests indicated no differences in the magnitude of adaptation in F2 either at the end of the learning phase or in the initial after-effect trials (end of learning: U = 549, p = 0.23, Cohen's d = 0.18; start of after-effect: U = 504, p = 0.43, Cohen's d = 0.12). In sum, both groups showed a significant increase in F2 value from baseline during learning, and no significant differences measured between the groups during the learning and after-effect phases.

### 4.3.3 Changes in F1-F2 vowel space

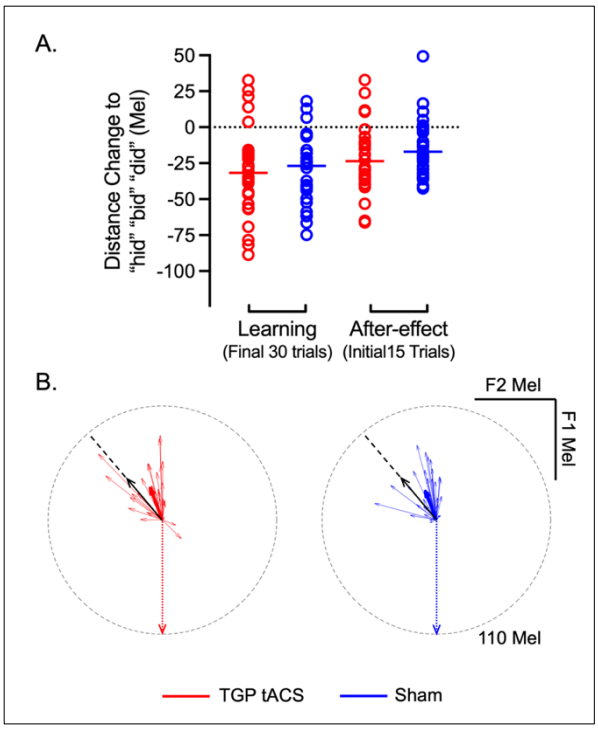



***Figure 4.4: Distance change in F1 and F2 towards "hid", "bid", and "did" in response to an upward F1 shift in feedback.*** *(A) The change in the Euclidean distance (measured in Mel within the F1-F2 space) between the baseline production of "head", "bed", and "dead" and the altered production, which shows that participants move their production closer to "hid", "bid", and "did". Refer to the legend in Fig. 4.2 for further information. (B) Red and blue vectors illustrate the compensatory adjustments in vowel production for TGP tACS and sham groups in the learning phase. Individual data are represented by thin vectors, while the thick vectors show the group average. The directions of the individual vectors were determined by their change in the participant's F1-F2 vowel space, and their magnitudes were adjusted by values in their normalised F1-F2 change. The black arrow indicates the required change direction from the vowel in the word "head" towards the vowel in "hid," and the dotted arrow shows the direction and magnitude of the formant shift (110 Mel) applied to feedback during learning. A light grey circle marks the 110 Mel extent of the applied shift, giving a reference to the size of the participants' adjustments.*

The combined adaptive changes in F1 and F2 in response to altered F1 feedback that were reported

in previous studies resulted in moving speech production closer to the production of an existing vowel in vowel space (Lametti et al., 2018; Tang et al., 2021) but stimulation over the left speech motor cortex did not affect this response relative to sham stimulation. To assess this in the current study, we calculated the Euclidean distance in F1-F2 vowel space between the productions of "head", "bed", and "dead" during the last 30 trials of the learning phase and the first 15 trials of the after-effect phase and productions of "hid", "bid", "did", "had", "bad", and "dad" during the vowel exploration phase. The change from baseline in the Euclidean distance between "head", "bed", "dead", and "hid", "bid", "did" in F1-F2 space during the learning phase is visualised in Fig. 4.5A while the Fig. 4.5B shows the magnitude and direction of production in F1-F2 vowel space. The magnitude of the combined F1-F2 change was compared between groups using a non-directional t-test. Each group reduced the distance between the two vowels in vowel space but the magnitude of these changes were not different between groups in either the learning phase ($t(59) = -0.63$, $p = 0.53$, Cohen's $d = -0.16$) or the after-effect phase ($t(58) = -1.14$, $p = 0.25$, Cohen's $d = -0.29$). Thus, TGP tACS had no effect on the magnitude or the direction of combined changes in F1 and F2 in response to the altered feedback.

### 4.3.4 Exploratory analysis on the after-effect phase

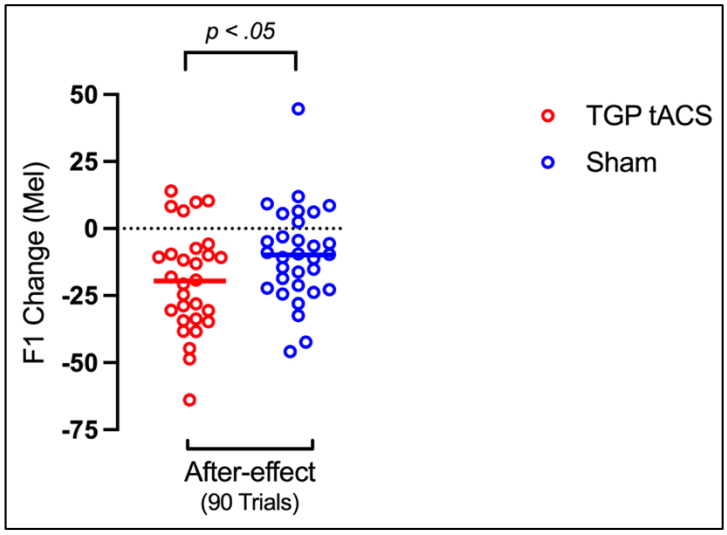



***Figure 4.5: Group differences in the after-effect phase.*** *F1 mean changes in all 90 utterances of the after-effect phase (trials 271-360) for both groups, TGP tACS and sham tACS. Statistically significant difference between groups are represented with the p-value. The colour coding remains the same that outlined in Fig. 4.2*

Inspection of Fig. 4.2A reveals a pronounced difference between the groups during the after-effect phase; the adaptive response in the TGP tACS group was slower to return to baseline when normal feedback was restored compared with the sham group. We tested this effect using a non-

directional two-sample t-test on the mean change in F1 frequency during this phase (see Fig. 4.3). A two tailed t-test revealed a statistically significant difference between the two groups throughout the after-effect phase ($t(58) = -2.02$, $p = 0.048$, Cohen's $d = -0.52$).

Upon examining Fig. 4.5, we identified a potential outlier in the sham group, with a maximum value of 44.634. To determine the range of typical values, we calculated the bounds within three 3SD from the mean ($M = -9.89$, $SD = 17.71$), resulting in a range from -63.028 to 43.238. The maximum value of 44.634 slightly exceeds this upper bound, classifying it as an outlier. It is important to note that, when we excluded the outlier there was a significant change in the results ($t(57) = -1.76$, $p = 0.08$, Cohen's $d = -0.45$). Despite this, the data point was collected accurately, and therefore, there is no justifiable reason to exclude it from the analysis based on a statistical threshold. There were no other outliers in the data.

## 4.4 Discussion

In the present study, we evaluated the efficacy of a novel brain stimulation protocol, tACS with a 75-Hz gamma frequency coupled to the peak of a 6-Hz theta envelope, on sensorimotor learning in speech. We administered TGP tACS over the articulatory representation in the left M1 to investigate whether this would enhance the expected adaptation response to an upwards shift in F1 frequency during auditory feedback.

During the learning phase, participants in both the TGP tACS and sham groups modified their speech production by reducing their F1 and increasing their F2 values. However, only the TGP tACS group demonstrated a significant increase in F2 value from baseline. Contrary to our initial hypothesis, no significant differences were observed between the groups regarding adaptation to the upwards F1 shift in auditory feedback at the end of the 30 learning phase trials or at the first 15 trials of the after-effect phase. Euclidean distance analysis revealed that the cumulative adjustments in F1 and F2 frequencies, which contributed to the speech production's approximation to a target vowel in the vowel space, were similar across groups.

In an exploratory analysis examining all 90 trials throughout the entire after-effect phase, a noteworthy difference emerged between the groups in terms of F1 adaptation. Specifically, the mean F1 value for the TGP tACS group was significantly lower than that for the sham group. This finding suggests that the administration of TGP tACS during a speech adaptation task might potentially improve the durability of learning. Furthermore, it implicates theta-gamma activity may be a crucial mechanism in reinforcing the persistence of sensorimotor learning in speech. However, this effect was sensitive to data variability, as excluding a single outlier in the sham group made the group difference non-significant. The outlier was retained in the analysis because it was collected accurately. Nonetheless, this highlights the need for caution in interpreting the exploratory findings, as they may reflect variability within the dataset rather than a robust effect. Future studies with larger samples and additional replication are necessary to validate these preliminary results and further investigate the potential for TGP tACS to improve the retention of motor learning in speech.

### 4.4.1 No group differences in the final 30 learning and the initial 15 after-effect trials

Our findings revealed that administering TGP tACS to the speech motor cortex in the left M1 did not result in a significant difference in the magnitude of F1 and F2 adaptations, compared with the sham tACS group, in the final 30 learning and the initial 15 after-effect trials. This outcome stands in contrast to previous studies that have reported significant differences in F1 adaptation between sham and active groups during similar speech adaptation tasks using tDCS (Lametti et al., 2018; Scott et al., 2020). We believe that the differences in adaptation rates between sham groups in the current study compared with previous studies are a primary factor in explaining these varying outcomes. For instance, in the study of Lametti et al. (2018), the adaptation to the F1 feedback shift (+21% of baseline) was 29% for the active stimulation group and 10% for the sham group. Similarly, Scott and colleagues (2020) reported an adaptation of 28% for the active stimulation group and 23% for the sham group in response to the F1 perturbation (+30% of baseline). In contrast, in our study, the TGP tACS group showed approximately 31% adaptation to the introduced 110 Mel shift in F1 frequency, while the adaptation in the sham group was

around 28%. The adaptation magnitude in the sham group in our study was notably higher than in previous studies, with 10% in Lametti et al.'s study and 23% in Scott et al.'s study. Although the TGP tACS group exhibited a higher magnitude of adaptation than measured in sham group, the F1 value of the sham group which is relatively higher than those seen in previous research potentially diminished the significant differences between groups in our research. This suggests that the adaptation rate might have approached a learning boundary for this type of sensorimotor learning task, making it challenging to detect the modulatory effects of TGP tACS during the last 30 trials of learning and the first 15 trials of the after-effect phases.

The methodological difference in using TGP tACS instead of tDCS could contribute to the different outcomes from the previous studies. Our approach involved the application of tACS at a 75-Hz gamma frequency, synchronised with the peak of a 6-Hz theta envelope, aimed at enhancing speech adaptation effects, as previously reported for improving new motor skill acquisition (Akkad et al., 2021; Rustamov et al., 2022). Nonetheless, evidence supporting the efficacy of TGP tACS in improving sensorimotor learning in speech remains to be proven. While TGP tACS may facilitate the learning of simpler motor tasks, like thumb abduction (Akkad et al., 2021), its effectiveness for complex motor tasks such as speech production is not clear. There's also a possibility that the specific modulation of theta and gamma rhythms may not effectively enhance the acquisition of new motor skills within the speech motor cortex, where coordination among hundreds of muscles is required. The need for further studies that replicate these findings, coupled with individualised frequency modelling using EEG (Marchesotti et al., 2020) during speech production, may be useful to test these hypotheses.

Our use of a 2 mA current, oscillating from 1 mA peak anode to 1 mA peak cathode, is lower than the steady 2 mA peak tDCS current used in prior studies (Lametti et al., 2018; Scott et al., 2020). This might potentially result in a less potent stimulation for facilitating sensorimotor learning in speech. Another difference between our study and the previous study from Lametti and colleagues, is the placement of the cathode electrode. In the previous study, the cathode was positioned in a landscape configuration on the forehead above the right eye, while in our study,

the second electrode was placed over the Pz. However, our current flow simulation demonstrated that the distribution of current flow successfully targeted the speech articulators. Overall, we believe it's unlikely that neither the usage of TGP tACS instead of tDCS and nor our montage of electrodes account for the lack of observed modulatory effects on task performance in our study, especially since our stimulation group showed a larger adaptation in F1 compared with previous the two tDCS studies.

It's important to note that replicating the behavioural effects of facilitatory non-invasive brain stimulation in neurotypical populations has often proved challenging (Guerra, López-Alonso, et al., 2020). Transcranial electrical stimulation (tES) may demonstrate optimal efficacy in situations where the cortical region targeted for stimulation exhibits atypical functionality. This is exemplified in the context of dyslexia, where the phonological impairments are linked to disrupted low-gamma oscillatory activities within the left auditory cortex (Marchesotti et al., 2020). Selective 30-Hz tACS intervention, have shown to significantly enhance phonological processing and reading precision, with improvements being observable immediately post-intervention. In a parallel vein, application of tDCS has been found to improve fluency in people who stutter, further supporting the potential selectivity of tES effectiveness in atypical cortical functionality (Chesters et al., 2018; Moein et al., 2022). The absence of significant findings in our earlier hypothesis, might therefore be attributed to the optimal functioning of healthy young adults' neural systems, which could diminish the impact of TGP tACS modulation.

In tES studies, effects often become more pronounced after multiple sessions, as the neuroplasticity involved in repetitive training can induce changes over time in task specific manner (Reis et al., 2009; Saucedo Marquez et al., 2013). For instance, Saucedo Marquez and colleagues (2013) found that anodal-tDCS applied to the M1 area differently impacts learning and memory, depending on the task. Notably, anodal-tDCS over three consecutive days significantly enhanced learning in the sequential finger tapping task, while it only improved retention in the visual isometric pinch force task, in which participants aim to match their pinch grip force to a target level shown on a screen without moving their hand or fingers. Similarly, Reis and

colleagues (2009) observed that repeated tDCS applications over five consecutive days greatly improved skill acquisition in a similar pinch force task, with more substantial improvements by the fifth day. Moreover, Chesters and colleagues (2017) observed no significant effects following a single session in a within-subject cross-over design involving people who stutter, yet a subsequent 5-day randomised controlled trial showed significant increase in speech fluency (Chesters et al., 2018). This highlights the importance of continuous, daily sessions in enhancing the consolidation of motor skills in healthy participants, suggesting that repetitive tES application can have larger effects on learning outcomes over time. Further research in sensorimotor learning in speech could benefit from this approach, with the application of tES over multiple consecutive days to make the analysis more sensitive to detect group differences.

Another effective approach would be the use of a within-subject design, as demonstrated in the study by Nitsche and colleagues (2003) which facilitated implicit motor learning through tDCS. In this design, each participant acted as their own control by receiving various stimulation conditions, namely anodal, cathodal, and sham. This approach would increase statistical power by reducing the impact of between-subject variability. This is especially relevant because, unlike in visuomotor adaptation studies where nearly every participant adjusts their behaviour after receiving incorrect feedback (Krakauer et al., 2000), a considerable portion of people in sensorimotor learning in speech research fail to show any adaptation when experienced changes in auditory feedback (Krakauer et al., 2000; Rochet-Capellan et al., 2011). However, implementing within subject design in sensorimotor learning for speech production presents challenges, as it needs to be considered that improvements in learning for speech are believed to persist for at least one month (Houde & Jordan, 2002).

TGP tACS group exhibited an adaptation in F2 frequency by approximately 11% in response to a 110 Mel shift in the F1 frequency, in contrast, the sham group showed a lesser adaptation at about 5%. Despite the two-times greater F2 adaptation measured in the TGP tACS group, no significant differences between groups were detected in the extent of F2 adaptation by the end of

the learning phase and the groups also did not differ in terms of their combined F1 and F2 changes in vowel space.

In summary, even though our study encompassing a larger sample size than previous speech adaptation studies using tDCS and possessing adequate statistical power, we believe that the number of trials, and the analytical focus on the last 30 utterances and the first 15 utterances of the after-effect phases for the F1 change may not be sufficiently sensitive to detect the neuromodulatory effects of TGP tACS in healthy participants.

### 4.4.2 TGP tACS enhances durability of sensorimotor learning in speech

Upon examining Figure 4.2A, we noticed a substantial difference in F1 values between the groups during the after-effect phase. To assess this difference, we conducted a non-directional t-test, which revealed that the mean value for the TGP tACS group was significantly lower than that of the sham group, indicating sustained learning effects. However, these results were not predicted and should be considered exploratory.

We interpret the enhanced durability of sensorimotor learning observed during the after-effect phase as a result of neuroplasticity effects induced by gamma stimulation at the peak of theta oscillations. This extended duration of speech motor learning aligns with previous findings that 75 Hz activity (gamma stimulation), particularly when synchronised with theta oscillations, is important for skill acquisition (Nowak et al., 2017). In hippocampal learning, the coupling of specific gamma frequencies, notably the 60-80 Hz range, with the peak of a theta wave associated with memory encoding (Lopes-dos-Santos et al., 2018). The phenomenon of theta-gamma phase-amplitude coupling is recognised not just in the hippocampus but across cortical areas, suggesting its foundational role in cortical computation (Alekseichuk et al., 2016; Fries, 2009; Lisman & Jensen, 2013). Supporting this, Akkad and colleagues (2021) have demonstrated the potential of 75 Hz stimulation, at the peak of 6 Hz oscillations, to enhance motor skill learning. Therefore, our choice of 75 Hz stimulation was influenced by its role in hippocampal learning and its

presence in motor cortex gamma activity at theta peaks (Canolty et al., 2006), as well as by positive evidence of its effectiveness in motor skill acquisition (Akkad et al., 2021).

The neurophysiological basis of this finding may stem from reduced GABAergic activity within the motor cortex, which is fundamental to motor plasticity (Clarkson et al., 2010; Stagg et al., 2009, 2011). Theta-gamma phase-amplitude coupling could potentially be a key driver of this neuroplasticity in motor learning (Nowak et al., 2017). Further research employing TGP tACS alongside a neuroimaging method such as magnetic resonance spectroscopy would be beneficial to understand the neurophysiology behind enduring effects of sensorimotor learning in speech.

Our finding of prolonged motor learning is consistent with research indicating that M1 plays a crucial role in maintaining acquired movement patterns once feedback disturbances are removed (Galea et al., 2011; Sale & Kuzovina, 2022; Yamaguchi et al., 2020). For instance, applying anodal tDCS to M1, did not influence the speed or accuracy of visuomotor adaptation but did enhance the durability of the adaptations in the absence of perturbations (Galea et al., 2011). A tACS study that investigated the effects of active 0.75 Hz stimulation on M1 during a ballistic thumb abduction motor training task found similar results (Sale & Kuzovina, 2022). The primary measure of interest was the change in thumb abduction acceleration, assessed immediately after training and again 24 hours later to evaluate short-term and longer-term training effects, respectively. Both active and sham stimulation groups showed an immediate increase in thumb acceleration following training, however, only the active tACS group demonstrated a significant enhancement in thumb acceleration 24 hours post-training, suggesting that 0.75 Hz tACS applied during motor training can improve the retention and possibly the efficiency of motor learning, leading to sustained long-term benefits. Another study found that beta-band tACS applied immediately after skill acquisition significantly improved motor skill retention over 1 and 7 days compared to a sham group, suggesting tACS on M1 enhances the consolidation of motor skills (Yamaguchi et al., 2020). Consequently, incorporating a 24-hour post-training assessment in future sensorimotor learning in speech studies could provide valuable insights into the enduring

effects of TGP tACS, highlighting its potential to facilitate long-term motor skill retention and enhancement.

The current study was aimed at testing the hypothesis regarding the impact of TGP tACS in sensorimotor learning of speech. While our focus was not on exploring other frequency couplings, it is important to note that gamma stimulation alone has been shown to facilitate learning (Asamoah et al., 2019; Moisa et al., 2016), though perhaps not to the extent observed with theta-gamma phase amplitude coupling (Alekseichuk et al., 2016). Additionally, an inverted waveform was used as an active control in a previous study in motor learning to control the effects attributable only to peripheral stimulation (Akkad et al., 2021).

We believe that the difference between groups during the after-effect phase is not simply due to increased variability in behavioural responses from TGP tACS, contrary to previous assumptions that non-invasive brain stimulation enhances behavioural variability and thus skill improvement (Teo et al., 2011). Rather, the learning trajectory during the stimulation was consistent across groups until the removal of the F1 perturbation, suggesting a direct influence of TGP tACS on the durability of learning (see Fig. 4.2A).

One might argue that TGP tACS inhibited the unlearning process (also referred as washout) during the after-effect phase, thereby causing group differences. However, this seems unlikely to account for the positive outcomes. If TGP tACS had an inhibitory effect, it should have been evident during the learning phase as well. As mentioned above, Tang and colleagues (2021) aimed to inhibit sensorimotor adaptation learning by applying rTMS over the left speech motor cortex. They showed that interfering on the tongue representation in M1 hindered the anticipated adaptation response for an upwards F1 shift in auditory feedback, specifically a decrease in F1 frequency with an increase in F2 frequency. Instead, in this current study, TGP tACS group adapted to approximately 31% of the introduced 110 Mel shift in F1 frequency, a larger change than the sham group's 28% adaptation. Additionally, the TGP tACS group showed an 11%

adaptation in F2 frequency for the same 110 Mel shift in F1 frequency, while the sham group's adaptation was about half of that, at 5%.

## 4.5 Conclusion

Our study explored the impact of TGP tACS on sensorimotor learning in speech by targeting the speech motor cortex. Contrary to our initial hypothesis and previous tDCS studies, we observed no significant differences between groups in adaptation for both the shifted (F1) and unshifted (F2) formants during the final 30 trials of the learning phase and the initial 15 trials of the after-effect phase. Our findings suggest that the lack of observed modulatory effects on sensorimotor learning may not be attributed to the use of TGP tACS in lieu of tDCS, particularly given that the adaptation in F1 within the sham group in a previous study was 10%, compared with 28% in the sham group of our study. In exploratory analysis, we found significantly reduced mean F1 values in the TGP tACS group throughout the after-effect phase, indicating an enhanced durability of sensorimotor learning in speech. This finding aligns with previous tACS studies that have shown an increase in the persistence of motor learning. It uniquely highlights the potential significance of theta-gamma coupling in improving the durability of speech motor learning. Nevertheless, these findings are preliminary and highlight the necessity for further research to confirm their reliability and understand the implications of TGP tACS on speech motor learning.

# 5

# A creative use of choral speech to eliminate stuttering during presentations

## Abstract

Choral speech, defined as speaking in unison with another voice, has long been recognised for its ability to enhance speech fluency while maintaining relatively natural speech quality for people who stutter. However, its practical application has been limited due to the need for a second voice and a reading material, restricting its use in real-life scenarios. In this study, we sought to investigate whether the fluency-enhancing effect of choral speech could be used in a presentation using self-recorded speech as the second voice. Based on prior research suggesting that many people who stutter demonstrate increased fluency when speaking alone, we asked participants to record their voice alone, which could then be played back through headphones during presentations to elicit the choral speech fluency-enhancing effect. Additionally, we tested a second choral speech condition in which participants synchronised their speech with a computer-generated voice. Baseline and control conditions included a presentation without intervention, and one accompanied by white noise, respectively. The results showed a substantial decrease in disfluent syllables, with the mean percentage dropping from 10% in the baseline condition to below 3% for both choral speech conditions, which is a threshold used to define clinical stuttering. Additionally, we observed a significant positive correlation between stuttering severity and the efficacy of choral speech with computer-generated voice, where those with the highest stuttering severity showed the largest reductions in disfluent syllables and reading duration during choral reading, suggesting that this method may be particularly beneficial for people with more severe stuttering. Importantly, the analysis of speech naturalness revealed no significant differences between conditions, highlighting that the method does not compromise the perceived naturalness of speech. This method holds promise as a practical tool for real-life situations, such as

presentations, where people who stutter could pre-write their speech and synchronise with a computer-generated voice through headphones, providing an option to reduce stuttering to near-absent levels.

## 5.1 Introduction

Public speaking is usually recognised as the most common fear in the general population (Daly et al., 1989; Dwyer & Davidson, 2012), which can result in intense state anxiety during the pre-speech period (Sawyer & Behnke, 1999). One of the greatest orators in history, Cicero, insightfully reflected on his own public speaking anxiety:

> *"I am always very nervous when I begin to speak. Each time I deliver a speech, I feel I am being judged, not only for my competence, but for my character and integrity" (Cicero, 1856).*

The anxiety of negative social evaluation, especially in speech-related situations, is more pronounced in people who stutter (PWS); for instance, 46% of adults who stutter suffer from social anxiety, compared with only 4% of matched controls (Blumgart et al., 2010). Social anxiety deriving from stuttering may lead to a cycle of stress and avoidance of public speaking situations. Avoiding public speaking can limit opportunities in both social and professional contexts. The current study focuses on utilising the highly effective fluency enhancer, known as choral speech, to provide an option for PWS to eliminate stuttering in public speaking with natural speech fluency.

Despite decades of research, no universally effective treatment for stuttering has emerged. Current therapeutic interventions often focus on fluency shaping techniques, which aim to modify speech patterns through behavioural training. These techniques typically involve slowing speech, extending vocal gestures to smooth transitions and managing breath control to regulate airflow during speech (Ingham & Andrews, 1973; Webster, 1980; see a systematic review: Brignell et al., 2020). However, these approaches tend to disrupt the natural rhythm and tone of speech (Tasko et al., 2007), which can result in high relapse rates as many people resort to their natural rhythm and tone. In recent years, there has been growing interest in brain stimulation techniques as a means of promoting neuroplasticity to support natural fluent speech. Early research in this area is promising, but the protocols for such treatments remain in the experimental stage, and their long-term efficacy is not yet well understood (Busan et al., 2019, 2021; Chesters et al., 2018; Garnett et al., 2019; Moein et al., 2022).

Temporary fluency enhancement can be achieved immediately through techniques that either provide external sensory feedback or allow the person who stutters to self-direct their speech. In the former category, the fluency enhancement is temporary because the effects disappear once the sensory feedback ends. This is analogous to using corrective glasses to improve eyesight: the effect is present only while the glasses are worn. Delayed auditory feedback (DAF), which plays back the speaker's voice with a slight delay, and frequency-altered feedback (FAF), which modifies the pitch of the voice, both have been shown to reduce stuttering to some extent (Andrew et al., 1996; Howell et al., 1983; Saltuklaroglu et al., 2009) though this reduction can come at the expense of distorting the natural rhythm and tone of speech, particularly in the case of DAF. Metronome-paced speech, in which the speaker aligns their syllables or words with a steady rhythm, has been found to be effective at eliminating stuttering (Fransella & Beech, 1965; Howell & El-Yaniv, 1987) as well but can severely disrupt prosody. In contrast, choral speech, where a person who stutters speaks in unison with another speaker, offers a more natural way of reducing stuttering (Saltuklaroglu et al., 2009; Virginia, 1939). One study demonstrated that choral speech can almost completely eliminate stuttering, achieving fluency improvements of up to 98%, whereas altered auditory feedback reduced stuttering by approximately 68% compared with normal auditory feedback (Saltuklaroglu et al., 2009). This is achieved without the need for extensive training, and the effect is immediate (Kalinowski & Saltuklaroglu, 2003). However, the need for another speaker to assist as the synchronising voice presents a significant practical barrier to the widespread use of choral speech in real-life scenarios. To address this limitation, our research investigates whether choral speech can be adapted for use in a presentation context by replacing the live second speaker with a pre-recorded voice or a computer-generated voice.

Another way to dissipate stuttering is an intriguing phenomenon: PWS do not stutter when speaking to themselves (Jackson et al., 2021). In one study, Jackson and colleagues (2021) reported no instances of stuttering in over 10,000 syllables produced during private speech. It is worth noting that, in private speech, participants engaged in self-directed speech while performing a task alone, with no intention of communicating with others. In that sense, private speech is

different from speaking alone if there is any communicative intention, such as recording voice that may be heard by others. In a survey of 1,649 PWS, 66% reported complete fluency when alone, with another 27% noticing significant improvement, while just 2.6% saw no change (Rasskazov & Rasskazova, 2007). These results suggest that stuttering is not only a speech-motor issue but is also modulated by psychological factors including the presence of an audience and mentalising on the audience's expectations, hesitancy of accurate and appropriate information transfer, negative self & social evaluation, and time pressure (Jackson et al., 2016; Jon & Esther, 1945; Quarrington, 1965; Sheehan et al., 1967; see Alm, 2014 for a review). Based on these findings, we proposed to investigate whether PWS could pre-record their speech fluently when alone and later use their own recording to engage in choral speech during a presentation task with an improved fluency.

Therefore, in the current study, we asked participants to first record their voice while alone and later read the same text in unison with their recorded voice through headphones, in the presence of a researcher. As an alternative, we also tested a text-to-speech system, where participants synchronised their speech with a computer-generated voice coming through headphones. In the experimental design, two control conditions were used: reading without sensory feedback and reading while listening to white noise, as masking noise has also been shown to reduce stuttering (Adams & Hutchinson, 1974). Our research centred on one key question: Can people PWS deliver a stutter-free presentation by performing choral speech with their own pre-recorded voice? Further, we asked how this compared with performing the same task using a computer-generated voice, which would be a practical solution for participants who would stutter when reading alone. We also measured the naturalness of speech, with the prediction that performing choral speech with one's own voice would result in higher naturalness because people synchronise their voice with their own natural rhythm, including breathing, pauses, and pace. Much like public figures, such as presidents, news anchors, or even kings, who read from pre-written texts, we believe this method offers ecological validity and presents a practical tool for delivering speeches fluently.

Moreover, it provides the flexibility for individuals to prepare and use their own speech, that aligns with real-world demands for presentations, public speaking, and teaching.

## 5.2 Methodology

### 5.2.1 Participants

Our sample size was exploratory due to the absence of an available effect size. However, Saltuklaroglu and colleagues (2009) reported a significant reduction in stuttering (approximately 98%) with a sample of 10 participants when they engaged in choral speech. Based on these findings, we believe that including 14 PWS was sufficient to achieve a comparable effect. Of these, 11 participants had received formal diagnoses from either a doctor or a speech therapist, while the remaining three self-reported their stuttering condition based on their own assessment. Recruitment was carried out through online advertisements on the British Stammering Association's website and social media accounts, and through the Oxford Stammering Support Group. Ethical approval was granted by the University of Oxford Central University Research Ethics Committee (MS-IDREC-2023).

The participants, aged between 18 and 35 years (mean age = 27), were all native English speakers with normal hearing and no language or speech impairments other than stuttering. Seven were female, and one identified as left-handed. Only one participant was undergoing therapy at the time of testing, although 12 reported prior therapeutic interventions.

### 5.2.2 Procedure

Before the experimental visit, participants were instructed to record themselves reading a provided text (information about the text is detailed below). An example voice recording (using a different text, recorded by the author) was sent to them, and these participant recordings were later analysed as the Recording Alone condition. Participants were not informed of the specific purpose of the recording. The instructions were sent via email and read as follows: "We kindly ask you to make an audio recording of yourself reading the attached story (Antarctic) before your visit to the department. Please ensure that you are alone while making the recording, with no

audience or anyone else who can hear you. You may re-record yourself as many times as needed until you are satisfied with the result. Please use a natural speaking rate that feels comfortable to you (an example recording is attached). You may email the recording to us prior to your visit, or bring it with you on a USB stick."

The experiment was designed as a single-session visit, spanning about one and a half hours. Upon their visit, speech samples were collected initially through reading and spontaneous question-answering tasks, with video footage used to measure baseline stuttering levels using the Stuttering Severity Instrument version 4 (Riley, 2009). The study involved delivering presentations and was concluded with a semi-structured interview. The interview data is analysed in detail in the Exploratory Qualitative Analysis section of this paper.

Participants were asked to read a 655-syllable text with a readability level appropriate for a 15.5-year-old, which incorporated scientific terminology related to Antarctic research and glaciology. Each participant was instructed as follows: "Imagine you are a news presenter preparing to deliver the latest update from the British Antarctic Survey for the BBC-4 channel. You will read this passage four times, each time using a different approach". Before the experiment starts, participants completed at least one training session with shorter texts (between 200 to 400 syllables), using both choral speech with a human voice recording and with the computer's voice separately. This provided familiarity with the experimental conditions. Participants were instructed to synchronise their speech word-by-word with what they heard but were informed that minor deviations, such as missing or shadowing the recording, were acceptable. They were encouraged to follow the approach that felt most comfortable to them.

During the experiment, participants read the text under four conditions presented in a 4 different randomised order across participants: (A) normal reading without sensory feedback (Reading), (B) choral reading with the participant's own voice recording (ChoralR), (C) choral reading with a computer-generated voice (ChoralC), and (D) reading with white noise (ReadingWN). Participants assigned to Order A performed the tasks in the sequence A, B, C, D, while those in

Order B followed the sequence B, C, D, A, and so forth for the remaining orders. Between conditions, participants were given at least a one-minute break to minimise fatigue.

**A) Normal reading condition (Reading)**

In this condition, participants read the text aloud as if presenting to an audience, while positioned in front of a camera and researcher, as was the case in all conditions. They wore headphones throughout to control for any effects related to wearing headphones, although no auditory feedback was provided.

**B) Choral reading with participant's own voice recording (ChoralR)**

Here, participants read the text while synchronising their speech with their own pre-recorded voice reading the same text while alone, which was delivered through headphones. The volume of the recording was adjusted to a comfortable listening level using the researcher's judgment before the session began to help maintain consistency across participants.

**C) Choral reading with a computer-generated voice (ChoralC)**

Participants were asked to read the text in unison with a computer-generated voice created using the Microsoft Word's Read Aloud function. The pace of the synthetic voice was set at a speed chosen by the participants, who were advised to select a slightly slower pace than their typical fluent speech, as the computer-generated voice was unfamiliar to them. Female participants listened to the same female voice, and male participants listened to the same male voice. The volume was standardised across participants using the same laptop, volume settings, and software.

**D) Reading with white noise condition (ReadingWN)**

In this condition, participants read the text while listening to white noise through their headphones. To avoid the Lombard effect (Lombard, 1911) where speakers unintentionally raise their voice in response to masking noise, participants were instructed to maintain a natural volume. The white noise was set at 60 decibels, based on previous findings where 50 decibels of white noise reduced stuttering by nearly half (Adams & Hutchinson, 1974; see a computational

model: Civier et al., 2010). This level was selected with the additional consideration that it should allow the speaker to still hear any potential questions during a presentation.

### 5.2.3 Experimental Setting

The recording of the session was conducted using both video and audio. A camera (Panasonic HC-V180) was placed at eye level in front of the participant, capturing the upper body and face to observe physical concomitants knowns as secondary behaviours of stuttering, such as involuntary eye blinking or head movements. Audio was recorded using a lapel microphone connected to this camera, while a secondary microphone (Samson C01UPRO) was connected to a laptop running Audacity software to serve as an audio backup. Participants wore over-ear headphones (Sony MDR-ZX110NA) through which they listened to recordings or the computer-generated voice played via a Lenovo Windows laptop.

### 5.2.4 Statistical Analysis

The percentage of disfluent syllables (%ds) was calculated for each of the four conditions by dividing the number of stuttered syllables by the total number of syllables produced in each trial, using the following formula: (Total number of disfluent syllables/Total number of syllables) x 100. The author, who conducted the study, manually analysed the disfluent syllables. Stuttering was defined as blocks, prolongations, part and whole word repetitions, and interjections (e.g., “hmm”; “err”), which were considered as avoidance behaviours indicative of stuttering (e.g., Ramitha et al., 2024; Sheikh et al., 2024; Kourkounakis et al., 2020; Lea et al., 2021), however, whole word repetitions and interjections were not counted as stuttering during SSI-4 analysis (Riley, 2009). The SSI-4 combines measures of frequency, duration, and physical concomitants to provide a comprehensive severity score. Frequency is calculated as the %ds during reading and conversational tasks. Duration is based on the average length of the three longest stuttering events, and physical concomitants are rated on a 0 to 5 scale.

The distribution of %ds across experimental conditions was assessed for normality using the Shapiro-Wilk test. Results revealed non-normal distributions in all conditions ($p < 0.05$), violating the assumptions of parametric statistical tests. Therefore, the Friedman test, a non-parametric alternative to repeated-measures ANOVA, was carried out to evaluate differences in %ds across the conditions. This test ranks the data and compares the distributions across related groups, which makes it suitable for analysing repeated-measures data with non-normal distributions. Pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction to adjust for multiple comparisons.

To investigate the effects of Rec. Alone (see Table 5.2), a non-parametric Wilcoxon signed-rank test was conducted to determine whether this condition significantly reduced %ds compared with Reading.

To examine the relationship between stuttering severity and stuttering reduction across different speech conditions, the reduction in %ds was calculated by subtracting the %ds of each sensory feedback condition (ChoralR, ChoralC, and ReadingWN) from the %ds of the baseline Reading condition. Spearman correlation was used to assess the relationship between stuttering severity (measured by Total SSI scores) and reduction in %ds within each condition. This non-parametric method was chosen for its robustness to non-normality and outliers. A Bonferroni correction was applied to the resulting p-values.

We also explored the relationship between stuttering severity and reading durations. Reading duration was measured as the total time from the first utterance to the last in each condition. Since the data did not meet the assumption of normality, as determined by an initial Shapiro-Wilk test, a Friedman test was used to analyse reading durations across the four conditions, as it was used for the disfluency analysis. Subsequently, we looked at the correlation between the reduction in reading durations and stuttering severity to assess their relationship across conditions. As with previous analyses, a Bonferroni correction was applied.

To assess the reliability of the SSI-4 scores, inter-rater reliability was evaluated by having a second researcher independently analyse the data for the first seven participants (50% of the sample). Intra-rater reliability was assessed by having the first author reanalyse the same seven participants' data after a minimum interval of one week. Reliability was quantified using the intraclass correlation coefficient (ICC) (Koo & Li, 2016). ICC values were interpreted based on established guidelines: <0.50 as poor, 0.50 to 0.75 as moderate, 0.75 to 0.90 as good, and >0.90 as excellent reliability (Koo & Li, 2016).

Speech naturalness was evaluated by a researcher with C2 level of English proficiency (highest score that can be achieved), as certified by The International English Language Testing System (IELTS), who had learned English from childhood. The researcher was completely blinded to the study's aims and the conditions under which the speech samples were collected. Immediately after listening to each sample, the researcher rated its naturalness based on how closely the speaker's speech aligned with the demographic norms of typical speakers (Riley, 2009). This evaluation was conducted using a nine-point scale, where 1 indicated highly natural-sounding speech and 9 represented highly unnatural-sounding speech. A linear mixed-model was employed to analyse the Likert scale data, with condition set as a fixed effect and participant as a random effect, to assess differences in ratings across the conditions.

In cases where participants skipped certain syllables, these missing syllables were subtracted from the total read syllables, and the percentage of stuttered syllables was calculated based on the adjusted syllable count specifically for each participant. Additionally, the percentage of missing syllables was calculated for each condition.

## 5.3 Results

The mean total SSI-4 score across participants was 26.07, with a range spanning from 11 to 50 (see Table 5.1). Based on these scores, participants were categorised into four severity levels: 1 was classified as having very mild stuttering, 6 as mild, 4 as moderate, and 3 as very severe. Two participants, P13 and P14, who were classified as having very severe stuttering, did not complete

the ChoralR condition. This decision was made because their %ds in their Rec. Alone was 25.27% and 23.98%, respectively (see Table 5.2). These high disfluency rates indicated that synchronising with their own recorded voice would not have produced a reliable choral effect, as the stuttering was too severe during recording to benefit from the auditory feedback in this condition. Additionally, data is missing for the ReadingWN of P10 due to a technical problem.

A total of 9,193 syllables were analysed in the Reading condition (14 participants: 5 missed syllables, 947 stuttered), 7,832 in the ChoralR (12 participants: 52 missed, 188 stuttered), 9,130 in the ChoralC (14 participants: 68 missed, 184 stuttered), and 8,538 in the ReadingWN (13 participants: 3 missed, 870 stuttered). Descriptive statistics for %ds across conditions showed that in both ChoralR and ChoralC, the mean and median %ds fell below the conventional 3% threshold, which is commonly regarded as the level distinguishing typical fluency from stuttering (Gordon & Luper, 1992). For Reading, the median (IQR) %ds were 5.93 (1.45 to 12.09); for ChoralR, 1.67 (1.29 to 3.25); for ChoralC, 1.15 (0.76 to 1.52); and for ReadingWN, 5.78 (0.91 to 13.55) (see Table 5.2, Figure 5.1). The mean (SD) %ds were 10.29 (13.82), 2.40 (1.76), 2.01 (3.48), and 10.19 (13.88), respectively.

| Participant | Reading | Speaking | Duration | Physical Concomitants | Total | Severity |
|---|---|---|---|---|---|---|
| P05 | 4 | 3 | 2 | 2 | 11 | very mild |
| P06 | 6 | 3 | 8 | 2 | 19 | mild |
| P08 | 4 | 2 | 10 | 3 | 19 | mild |
| P09 | 7 | 2 | 8 | 2 | 19 | mild |
| P10 | 7 | 3 | 6 | 4 | 20 | mild |
| P11 | 7 | 2 | 8 | 4 | 21 | mild |
| P04 | 6 | 5 | 3 | 10 | 24 | mild |
| P01 | 5 | 5 | 10 | 5 | 25 | moderate |
| P07 | 8 | 5 | 10 | 3 | 26 | moderate |
| P12 | 7 | 8 | 8 | 3 | 26 | moderate |
| P03 | 6 | 4 | 12 | 6 | 28 | moderate |
| P02 | 9 | 8 | 12 | 9 | 38 | very severe |
| P13 | 9 | 8 | 12 | 10 | 39 | very severe |
| P14 | 9 | 8 | 19 | 14 | 50 | very severe |
| **mean** | **6.71** | **4.64** | **9.14** | **5.54** | **26.07** | **moderate** |

***Table 05.1: SSI-4 scores based on four subcategories: reading, speaking, duration of the longest three stuttered moments, and physical concomitants.*** *The total score is derived from these subcategories and used to classify stuttering severity as mild, moderate, severe, or very severe. The data represent both the*

*range and average scores across participants. Mean values are calculated for each category at the bottom. SSI: Stuttering severity index.*

The distribution of the %ds across conditions was assessed using skewness and the Shapiro-Wilk test. Severe skewness was seen for ChoralC (3.12), while ReadingWN, Reading, and ChoralR showed moderate skewness (1.51, 1.85, and 1.20, respectively). The Shapiro-Wilk test confirmed non-normality for all conditions ($p < 0.05$). Consequently, non-parametric statistical methods were employed to account for the non-normal distribution of the data.

A Friedman test revealed significant differences in the %ds across the four conditions (chi-squared = 9.76, df = 3, W = 0.3, p = 0.02). Pairwise comparisons of the %ds between conditions using the Wilcoxon signed-rank test revealed significant differences after Bonferroni correction. The %ds for Reading was significantly higher than for ChoralC ($W = 101$, $p < 0.01$), but not significantly different from ChoralR ($W = 58$, $p = 0.88$) or ReadingWN ($W = 56$, $p = 1.00$). Although ChoralR and ChoralC showed close median values, the test detected a significant difference ($W = 77$, $p < 0.001$) due to the consistent direction of paired differences across participants, with ChoralR generally showing higher %ds than ChoralC. In contrast, ChoralR and ReadingWN did not differ significantly ($W = 21$, $p = 1.00$), while the comparison between ChoralC and ReadingWN approached significance before correction ($W = 12$, $p < 0.02$) but did not remain significant after adjustment ($p = 0.10$). Overall, these results showed that ChoralC significantly reduces disfluency compared with Reading and ChoralR conditions.

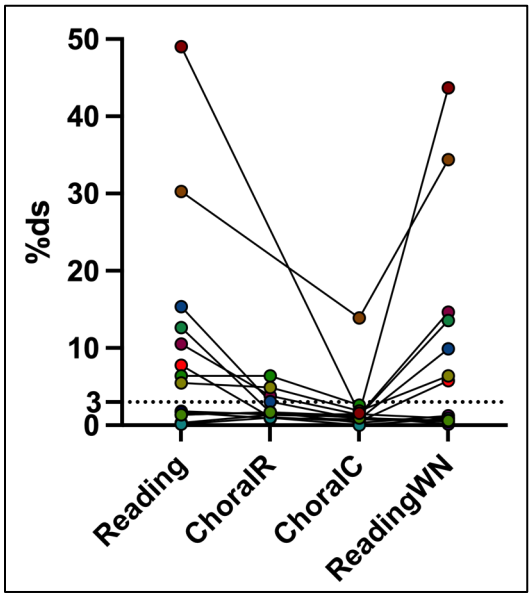



***Figure 5.1: Percentage of disfluent syllables by experimental condition.*** *The graph illustrates the percentage of disfluent syllables (%ds) across four conditions: Reading (Median = 5.93, IQR = 1.45 to 12.09); ChoralR (Median = 1.67, IQR = 1.29 to 3.25); ChoralC (Median = 1.15, IQR = 0.76 to 1.52); and for ReadingWN (Median = 5.78, IQR = 0.91 to 13.55). Each coloured dot represents an individual participant. The dotted line represents the conventional 3% threshold, which is commonly used to differentiate typical fluency from stuttering. Reading: normal reading condition; ChoralR: Choral reading with participant's own voice recording; ChoralC: Choral reading with a computer-generated voice; ReadingWN: Reading with white noise condition.*

The median (IQR) reduction in stuttering from the Reading condition (Figure 5.2) was greatest in the ChoralC condition 3.70 (0.56 to 10.84), followed by the ChoralR condition 0.5 (-0.30 to 6.69), with the smallest reduction observed in the ReadingWN condition 0.15 (-0.91 to 1.21) (Figure 5.2).

A Spearman correlation revealed a significant positive relationship between Total SSI scores and stuttering reduction in the ChoralC condition (rho = 0.70, p = 0.01), indicating that participants with higher stuttering severity experienced greater reductions in disfluencies in this condition. A moderate positive correlation was observed in the ChoralR condition (rho = 0.53, p = 0.22), though this did not reach statistical significance. In the ReadingWN condition, no meaningful correlation was found (rho = 0.16, p = 1). All p-values were Bonferroni-adjusted.

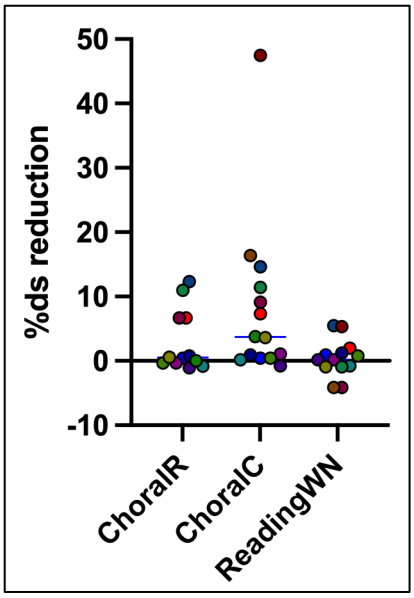



***Figure 5.2: Reduction in disfluent syllables across conditions.*** *The figure shows the reduction in %ds for each condition, with coloured dots representing individual participants (using the same colours as in Fig. 1) and blue lines indicating the medians. The greatest median reduction in stuttering from the Reading condition was observed in the ChoralC condition (Median = 3.70, IQR = 0.56 to 10.84), followed by ChoralR (Median = 0.5, IQR = -0.3 to 6.69), with the smallest reduction seen in ReadingWN (Median = 0.15, IQR = -0.91 to 1.21). Spearman correlation analysis revealed a significant positive relationship between Total SSI scores and stuttering reduction in the ChoralC condition (rho = 0.70, p = 0.01), while no significant correlations were observed for ChoralR (rho = 0.53, p = 0.22), or ReadingWN (rho = 0.16, p = 1).*

| **Par.** | **Reading** | | | **ChoralR** | | | **ChoralC** | | | **ReadingWN** | | | **Rec. Aln.** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | %ds | Rd. Dur. | Nat. | %ds | Rd. Dur. | Nat. | %ds | Rd. Dur. | Nat. | %ds | Rd. Dur. | Nat. | %ds |
| P01 | 1.8 | 2.4 | 6 | 1.41 | 2.4 | 8 | 1.4 | 2.5 | 6 | 0.9 | 2.2 | 2 | 0.6 |
| P02 | 7.76 | 3.5 | 7 | 1.1 | 3.3 | 5 | 0.5 | 3.3 | 3 | 5.8 | 3.3 | 6 | 5.5 |
| P03 | 10.5 | 5.6 | 8 | 3.81 | 5.1 | 7 | 1.4 | 3.1 | 3 | 14.6 | 7.2 | 9 | 7.1 |
| P04 | 1.37 | 3.2 | 4 | 1.7 | 3.5 | 5 | 0.3 | 4.1 | 3 | 1.2 | 2.9 | 3 | 7 |
| P05 | 0.3 | 3.1 | 2 | 1.4 | 3.2 | 4 | 1.1 | 4.1 | 6 | 0.1 | 2.9 | 3 | 1.5 |
| P06 | 1.67 | 2.9 | 3 | 0.9 | 3.2 | 4 | 0.8 | 4.1 | 5 | 0.5 | 3.9 | 2 | 0.1 |
| P07 | 15.4 | 5.3 | 9 | 3.0 | 4.5 | 6 | 0.8 | 4.1 | 5 | 9.9 | 4.4 | 8 | 6.8 |
| P08 | 0.15 | 2.3 | 3 | 1 | 3.5 | 5 | 0 | 2.3 | 2 | 0.9 | 2.4 | 2 | 0 |
| P09 | 12.6 | 3.2 | 8 | 1.7 | 2.3 | 3 | 1.2 | 4.1 | 6 | 13.5 | 2.8 | 7 | 1.5 |
| P10 | 6.4 | 3.2 | 8 | 6.4 | 3.1 | 6 | 2.6 | 3.5 | 7 | NA | NA | NA | 7.6 |
| P11 | 1.4 | 2.4 | 2 | 1.7 | 2.4 | 4 | 0.9 | 4.1 | 5 | 0.6 | 2.5 | 3 | 2.3 |
| P12 | 5.5 | 3.2 | 6 | 4.9 | 4.0 | 8 | 1.9 | 3.5 | 7 | 6.3 | 3.1 | 5 | 6.8 |
| P13 | 30.3 | 8.5 | 9 | NA | NA | NA | 14 | 4.0 | 7 | 34.4 | 9.4 | 9 | 25.3 |
| P14 | 49 | 19.5 | 9 | NA | NA | NA | 1.5 | 4.1 | 4 | 43.7 | 14.3 | 9 | 24 |
| **median** | **5.93** | **3.22** | **6.5** | **1.67** | **3.27** | **5** | **1.15** | **4.04** | **5** | **5.78** | **3.08** | **5** | **6.16** |

***Table 05.2: Percentage of disfluent syllables and reading duration across four experimental conditions.*** *This table presents the percentage of disfluent syllables (%ds), reading durations (Rd. Dur: in minutes) and speech naturalness (Nat.) for each participant (Par.) across five conditions: Reading, choral reading*

*with recording of participant's own voice (ChoralR), choral reading with computer-generated voice (ChoralC), reading with white noise (ReadingWN), and recording voice while reading alone (Rec. Aln.). Participants' disfluency rates were measured as the percentage of stuttered syllables per total syllables and reading duration was measured from the beginning to the end of each trial. Speech naturalness was evaluated using a nine-point scale, with 1 indicating highly natural speech and 9 indicating highly unnatural speech. Missing data are indicated where applicable. Median values for each condition are provided at the bottom of the table.*

For Rec. Alone, the mean (SD) %ds was 6.88 (8.05) slightly lower than the baseline Reading mean of 10.29 (13.82). However, the median %ds of Rec. Alone was slightly higher at 6.17 (1.52 to 7.11) compared with the baseline Reading median of 5.94 (1.44 to 12.09). Shapiro-Wilk tests indicated that both conditions deviated significantly from normality (Rec. Alone: $W = 0.74$, $p < 0.001$; Reading: $W = 0.73$, $p < 0.001$). Consequently, a non-parametric Wilcoxon signed-rank test revealed no significant difference between the two conditions ($W = 27$, $p = 0.12$).

The median (IQR) reading duration was longest in ChoralC, 4.04 (3.34 to 4.10), followed by baseline Reading, 3.22 (2.93 to 4.83); ChoralR, 3.27 (2.93 to 3.65); and ReadingWN, 3.08 (2.79 to 4.45). The Shapiro-Wilk normality test showed significant deviations from normality for Normal Reading ($p < 0.001$), ChoralC ($p = 0.003$), and ReadingWN ($p < 0.001$), while the ChoralR condition did not show a significant deviation from normality ($p = 0.38$). A Friedman test revealed no significant differences in durations across the four conditions (chi-squared = 2.89, df = 3, $W = 0.09$, $p = 0.41$).

When we analysed reductions in reading durations from baseline Reading, the median (IQR) scores were: ReadingWN, 0.20 (-0.16 to 0.32); ChoralR, 0.02 (-0.29 to 0.25) and ChoralC, -0.19 (-0.87 to 0.92) with no significant differences were observed between them (chi-squared = 2.18, df = 2, $W = 0.10$, $p = 0.34$). However, when we examined the Spearman correlation between Total SSI scores and reductions in reading duration across the three conditions, we observed a significant correlation in ChoralC (cho = 0.77, $p < 0.01$). In ChoralR, we found a weak positive correlation (cho = 0.34, $p = 0.86$), which did not reach statistical significance. Similarly, no meaningful correlation was observed in ReadingWN (cho = 0.07, $p = 1$). As in the previous analysis, all p-values were Bonferroni-adjusted for the correlation analysis. Overall, reductions in reading durations showed no significant differences across conditions, but stuttering severity was

positively correlated with the reduction in reading duration when participants performed the reading with computer generated voice.

The first author analysed all the data related to stuttering rates and severity, and a second researcher independently analysed the data of the first 7 participants of the SSI-4 data. Inter-rater reliability was assessed using ICC, which demonstrated a high level of agreement between the two raters (ICC = 0.933, $P < 0.001$). The first author then repeated the SSI-4 analysis of the first seven participants after at least one week to assess intra-rater reliability. A strong ICC was found for the intra-rater measurements (ICC = 0.929, $P < 0.001$), indicating a robust consistency across repeated measurements.

For the speech naturalness test, the mean ratings for the conditions were as follows: Reading (M = 6.00, SD = 2.69), ChoralR (M = 5.42, SD = 1.62), ChoralC (M = 4.93, SD = 1.69), and ReadingWM (M = 5.23, SD = 2.89), with median scores ranging from 5.0 to 6.5. The linear mixed-model analysis revealed that there were no statistically significant differences in ratings between the ChoralC condition and the ChoralR (Estimate = 0.75, p = 0.30), Reading (Estimate = 1.07, p = 0.12), and ReadingWM (Estimate = 0.38, p = 0.59) conditions.

### 5.3.1 Exploratory qualitative analysis

When participants were asked whether they would consider using the methods tested in this study for presentations in real life, responses varied, reflecting a mix of enthusiasm and reservations. We categorised participants' answers into three groups: 1) likely to use, 2) neutral/unsure, and 3) unlikely to use. Ten participants (P02, P03, P04, P05, P06, P07, P09, P13, P14), particularly all three participants with very severe stuttering, expressed a high likelihood of adopting these methods in real-life situations such as presentations or wedding speeches (Table 5.3). Most of these participants preferred either ChoralC or ChoralR, with some expressing a preference for both methods. Three participants (P01, P11, P12) were neutral or unsure, expressing mixed feelings, due to discomfort with listening to their own voice or the challenge of synchronising speech with the computer's voice, which lacked natural breathing, prosody, and timing. Two of

the participants preferred ReadingWN and one could prefer either ChoralC or ReadingWN. Finally, two participants with mild stuttering (P08, P10) reported they were unlikely to use any of the methods.

| Participant | Severity | Preferred Methods | Response |
|---|---|---|---|
| P02 | Very severe | ChoralC | likely to use |
| P03 | moderate | ChoralC/ChoralR | likely to use |
| P04 | mild | ChoralC/ChoralR | likely to use |
| P05 | very mild | ChoralR | likely to use |
| P06 | mild | ChoralC | likely to use |
| P07 | moderate | ChoralC | likely to use |
| P09 | mild | ChoralR | likely to use |
| P13 | very severe | ChoralC | likely to use |
| P14 | very severe | ChoralC | likely to use |
| P01 | mild | ReadingWN | neutral/unsure |
| P11 | mild | ReadingWN | neutral/unsure |
| P12 | moderate | ChoralC/ReadingWN | neutral/unsure |
| P08 | mild | None | unlikely to use |
| P10 | mild | None | unlikely to use |

***Table 05.3: Participant responses to preferred methods and likelihood of use.*** *This table summarises participants' stuttering severity, their preferred fluency-enhancing methods (ChoralC, ChoralR, ReadingWN, or none), and their likelihood of adopting the methods for real-life situations. Responses were categorised as "likely to use," "neutral/unsure," or "unlikely to use." Participants with more severe stuttering generally showed a higher likelihood of using the methods, with a preference for ChoralC (see table 5.2 for details).*

## 5.4 Discussion

To our knowledge, these results represent the first data examining the potential of choral speech as a fluency enhancer in an everyday task such as delivering a presentation, using self-recorded speech or computer-generated voices. The fluency improvements observed in the choral conditions are consistent with previous research using choral speech, where stuttering rates dropped significantly. In the present study, the mean (10%) and median (5%) baseline reading %ds were reduced to below 3% for both choral conditions, which is a threshold commonly used to define clinical stuttering. Our data also highlight a positive relationship between stuttering severity and the efficacy of choral speech, particularly with a computer-generated voice: as stuttering severity increased, the reductions in %ds and reading duration in this condition became more pronounced, suggesting that this method may be especially beneficial for people with higher levels of stuttering. This finding is further supported by participants' self-reported preferences, as

those with higher stuttering severity showed an interest in using the computer-generated choral speech method in future presentations. Moreover, the analysis of speech naturalness showed no significant differences across conditions. The ability to reduce stuttering and reading duration under severe conditions without breaking natural quality of speech is promising, as it points to the versatility of this approach for PWS seeking fluency improvements in real life contexts.

As mentioned in the Results section, two participants (P13 and P14) were excluded from the choral reading with own voice recording condition due to their high stuttering levels during the Rec. Alone condition. This decision was based on the observation that their severe disfluencies in their recording would prevent a reliable choral effect, thus compromising the validity of the results for this condition. Although this exclusion introduces a limitation related to missing not at random data, it was necessary to maintain the integrity of the analysis. Importantly, this approach also enhances the ecological validity of the study, as it reflects the practical limitations faced by people with severe stuttering who may not be able to use a self-recorded voice for choral speech.

We believe that the inclusion of interjections in our stuttering classification enhances the precision of our analysis and reflects advancements in recent research in stuttering classification (e.g., Ramitha et al., 2024; Sheikh et al., 2024; Kourkounakis et al., 2020; Lea et al., 2021). Especially, in the context of our reading task, interjections such as “hmm” or “err” are unlikely to occur during fluent reading but may be used as avoidance strategies to bypass stuttering utterances, which provides critical markers of disfluency that might otherwise be missed. Therefore, marking interjections reduces the risk of false negatives and provides a more nuanced classification of stuttering behaviours.

### 5.4.1 Possible real-life implications

The current study suggests a significant relationship between stuttering severity and the effectiveness of choral speech computer-generated voice. In particular, people with higher stuttering severity experienced greater reductions in stuttering when practiced ChoralC, without any compromise to perceived speech naturalness. This pattern also extended to reading duration,

where ChoralC showed a pronounced reduction in reading duration in those with the most severe stuttering. Remarkably, participant 14, who scored at a very severe stuttering level on the SSI-4, reduced their disfluency from 49% to 2% and shortened their reading duration from ~19 minutes to ~4 minutes under the ChoralC condition compared with the baseline reading condition. These findings suggest that ChoralC has the potential to serve as a powerful fluency enhancer for people with greater stuttering severity (compare with other fluency enhancers: Saltuklaroglu et al., 2009). For example, in a possible real-life scenario, a person with severe stuttering could prepare their speech in advance for an upcoming presentation, input it into a speech-to-text decoder application in their phone, and then deliver the presentation while synchronising their speech with a computer-generated voice through wireless earphones. This method could significantly enhance fluency, potentially reducing stuttering to near-absent level while maintaining a natural-sounding speech.

The ChoralR condition was less effective for people with severe stuttering, which can largely be attributed to the fact that we did not continue with this condition for the two participants classified as having very severe stutter. Their high disfluency rates (P13: 25% disfluency; P14: 24% disfluency) rendered the recordings inadequate for providing the necessary feedback to facilitate successful choral speech. As the primary aim of this study was to explore optimal public speaking strategies for PWS, these results suggest that ChoralC may serve as a more suitable method for people with severe stuttering. However, it is important to consider a personalised approach when recommending methods, as some participants reported that the computer-generated voice in ChoralC lacked naturalness, especially in its omission of natural breathing pauses and natural prosody. This underscores the need for individualised solutions that balance fluency enhancement with comfort. Advances in artificial intelligence may soon allow text-to-speech decoders to produce more human-like prosody (Kaur & Singh, 2023), including natural breathing rhythms and potentially matching the user's voice tone, consequently improving the naturalness of computer-generated speech. Until such advancements are realised, ChoralC appears to be the most promising option for those with severe stuttering, while people with mild to moderate

stuttering may benefit from a choice between ChoralC and ChoralR based on personal preference and speaking context.

Our findings strongly support the application of choral speech in real-life settings, such as public presentations, teaching roles, or ceremonial speeches. Beyond the immediate benefits of fluency, we argue that this method can play an important role in reducing the social anxiety often associated with public speaking for PWS (Blumgart et al., 2010; Craig & Tran, 2014; Iverach et al., 2009; Iverach & Rapee, 2014). Achieving fluency in a high-stakes situation could play a role as an exposure therapy, foster positive experiences, potentially decreasing the long-term anxiety tied to public speaking. For example, a person who experiences anxiety about stuttering in front of an audience could use choral speech through wireless earphones, assisting them to deliver a fluent presentation and, over time, build confidence. However, while we advocate for this method as a practical fluency tool, much like using reading glasses, it is important to recognise that fluency alone in public speaking does not address the broader social and emotional dimensions of stuttering all together. The anxiety of negative judgment, embarrassment, and social rejection in spontaneous speaking situations remains deeply ingrained (Craig & Tran, 2014; Iverach et al., 2009; Iverach & Rapee, 2014; Yaruss, 2010). Thus, in parallel with temporary fluency interventions, further research should investigate therapeutic approaches to achieve permanent fluency in spontaneous conversations with natural speech quality and to mitigate the social anxiety associated with stuttering.

### 5.4.2 Neural correlates of choral speech

The precise neural mechanisms underlying choral speech remain outside the focus of this research. However, based on current literature, we can propose several plausible neural correlates. One theory highlights the engagement of mirror neuron systems (Kalinowski & Saltuklaroglu, 2003). Since disruptions in internal models may potentially cause stuttering, the external speech input during choral speech may facilitate fluent speech by activating mirror neurons. Another view suggests that choral speech temporarily bypasses the automatic internal motor command initiation circuit (Alm, 2004a), which will be the focus of this discussion.

To understand better the neural mechanisms behind choral speech, it is essential to reference one of the prevailing neurobiological theories of stuttering. This model attributes stuttering to deficits within the cortico-basal ganglia-thalamocortical network (Alm, 2004; Chang & Guenther, 2020; Civier et al., 2013), which is primarily responsible for selecting and initiating motor commands. Structural and functional anomalies in this network have been observed in PWS compared with controls (Chang et al., 2009; Sommer et al., 2002; Toyomura et al., 2011; Watkins et al., 2008). Given that choral speech makes use of the external pacing cues provided by the other voice (Kalinowski & Saltuklaroglu, 2003), it is plausible that this mechanism bypasses the malfunctioning internal cue system, by creating a rhythm effect (Azrin et al., 1968; Garnett et al., 2019; Virginia, 1939). This external rhythm may offer an alternative motor pathway, shifting control from the compromised initiation circuit to external cues, as seen in other movement disorders like Parkinson's disease (Thaut et al., 2001). For example, people with Parkinson's disease, who have dopamine-depleted basal ganglia, demonstrate improved gait pattern when provided with external cues, such as visual cues for step initiation during walking (Bagley et al., 1991; Glickstein & Stein, 1991). The improvement is thought to occur because control shifts from the automatic cortico-basal ganglia-thalamocortical loop to the goal-directed cortico-cortical network (Jahanshahi et al., 1995; Redgrave et al., 2010). However, stuttering may not be solely a motor command initiation issue affecting all motor effectors; there is increasing theoretical and empirical support suggesting that stuttering involves atypical activity in auditory-motor integration, impacting how sensory feedback coordinates with motor execution for speech (see Civier et al., 2010; Max et al., 2004; Max & Daliri, 2019 for more detailed discussions).

During speech production, the brain predicts the auditory outcome of each planned articulatory movement and sends this expected sensory information to the auditory cortex to help guide motor execution (Houde & Nagarajan, 2011; Niziolek & Guenther, 2013; Tourville & Guenther, 2011). This predictive mechanism allows the brain to compare the actual auditory feedback received during speech with the predicted outcome, making rapid corrections to motor output if necessary to maintain fluent speech. In stuttering, disruptions in this predictive process can lead to

mismatches between the expected and actual auditory feedback (Civier et al., 2010; Max et al., 2004; Max & Daliri, 2019). These mismatches may interfere with the proper functioning of the basal ganglia (Chang & Zhu, 2013; Houde & Nagarajan, 2011). When basal ganglia fail to properly initiate speech motor actions due to this mismatch, stuttering events can occur. Choral speech may help bypass these different patterns in the auditory-motor integration by providing a correct and a stable auditory signal, which offers external feedback that aligns with the speaker's auditory expectations. This external auditory input could help reduce the brain's reliance on the internal speech motor command initiation mechanism. As a result, speech becomes temporarily fluent, as the external auditory signal allows basal ganglia and cortical networks to coordinate motor commands more effectively without the interference of feedback mismatches.

Such an account aligns well with one of the key neural markers of stuttering, which is the decreased activation in auditory regions during speech production tasks (Brown et al., 2005; Budde et al., 2014). Fluency-inducing conditions, such as choral speech or fluency shaping, significantly alter this pattern. In fact, auditory cortical activity in PWS can rise to levels seen in fluent speakers, or even surpass them (Fox et al., 1996; Garnett et al., 2022; Toyomura et al., 2011). This increased activity in the auditory cortex suggests the brain's ability to leverage external input, that allows it to compensate for the disruptions in sensorimotor integration (Garnett et al., 2022). During choral speech, increased brain activity has been observed in the posterior superior temporal gyrus (Garnett et al., 2022; Toyomura et al., 2011), near the temporal-parietal junction, specifically referred as Sylvian-parieto-temporal area (Hickok, 2009; Hickok et al., 2003), which is thought to be important for integrating auditory and motor signals and converting auditory feedback into motor commands. Electrophysiological studies further supported this showing that pre-speech auditory modulation, the brain's adjustment of sensory regions in anticipation of speech, is diminished or absent in PWS (Daliri & Max, 2015, 2018; see a review: Max & Daliri, 2019). This diminished predictive ability likely explains why choral speech works so effectively: by providing consistent external auditory feedback, it helps to stabilise the atypical

patterns in the auditory-motor integration, assisting brain to bypass its internal predictions and produce fluent speech.

### 5.4.3 Explaining within and between individual variabilities in recording-alone condition: insights from threat conditioning

It has been long known that PWS tend to stutter to a lesser extent when alone compared with social situations requiring communicative intent (Gavin et al., 1982; Hahn, 1940; Jackson et al., 2021; Martin & Haroldson, 1988; von Krais Porter, 1939). Based on these findings, we hypothesised that participants in our study would experience improved fluency when recording their speech alone. Although the mean stuttering frequency showed a slight reduction (from 10% to 7%), a non-parametric test was conducted due to the non-normal distribution of the data, found no significant result difference between groups.

After being asked, some participants stated that they might have been more fluent if they had not submitted their recordings to the researcher. This observation is compatible with earlier research suggesting that simply the awareness of being recorded and the idea of an audience (in the future) can maintain some levels of stuttering (Hahn, 1940). Jackson and colleagues (2021) further demonstrated that stuttering was eliminated during a self-directed speech task, where participants spoke privately without communicative intent and were unaware of being recorded. This reinforces the idea that the perception of being listened to or anticipation of they would be heard, can act as a trigger for stuttering (Alm, 2014). In our study, this effect might have been present as well, as the act of recording likely triggered stuttering due to participants anticipating that their speech would eventually be judged, since they were instructed to send or bring their recordings to the researcher. This self-consciousness, “mentalising” the audience’s expectations, and potential negative social evaluation seem to trigger stuttering, is in consistent with the idea that social judgement, whether real or imagined, may play a role in stuttering.

The variability in stuttering rate observed across participants highlights a key challenge: why do some PWS eliminate stuttering in the Rec. Alone condition while others experience increased disfluency? For instance, one participant’s stuttering reduced from 13% to 2%, even with the

knowledge that their recording would be heard by the researcher (Table 2). Conversely, another participant's disfluency rose from 1% to 7%. The explanation of within and between individual variabilities could be that recording one's own voice may evoke a threat response in some individuals, but not in others. This idea resonates with the threat response framework proposed by Peters and Guitar (1991), which posits that stuttering may function as a freeze response, silencing vocal output when the brain detects communicative intention as a threat. This freeze response may be selectively applied to speech motor functions, as the brain associates a simple stuttering event (e.g., repetitions) as a threat, based on past negative experiences (e.g., negative social evaluation). While PWS can speak fluently in non-communicative contexts such as self-directed or private speech (Jackson et al., 2021), disfluencies emerge when conditioned threats are present. Higher-order conditioning processes could extend this threat association to novel kinds of communicative intent, such as recording one's voice, leading some PWS to experience stuttering even by pressing the recording button, especially if previous experiences of recording have been paired with negative self or social evaluation. Overall, the threat conditioning as a modulator of stuttering events may offer an explanation within and between individual variabilities about why some people increase disfluent stutter during recording their voice as recording elicits threat response for them (Participant 7) while some people can eliminate stuttering in their voice-recordings (Participant 9).

## 5.5 Limitations

One limitation of the study is that the Rec. Alone condition was assessed by using only audio recordings rather than video. This might have led to an underestimation of silent blocks, which are often harder to detect without visual cues of speech effort. Additionally, we were unable to ensure that participants were truly alone during the recording sessions, which could have influenced their level of fluency.

Another limitation is the small sample size, consisting of 14 participants, including 7 with moderate to very severe stuttering, who, as our data suggest, may benefit more from this method.

It is possible that a ceiling effect exists for people with mild stuttering, leaving little room for further enhancement of speech fluency through choral speech techniques. Future research can focus specifically on people with moderate to very severe stuttering to better account for individual variability within this group, such as by using AI to replicate person's natural speech tone and rhythm. Additionally, practicing choral speech, particularly by becoming accustomed to using headphones and adjusting factors like speed and volume to suit individual preferences, may help individuals exert less effort and achieve greater fluency improvements over time.

Furthermore, the analyses of stuttering rates and severity were conducted by the first author. While inter-rater and intra-rater reliability analyses demonstrated high consistency, the use of blinded raters would have further enhanced the robustness of the results by eliminating potential bias in scoring.

An unexpected finding was the lack of improvement in fluency during the white noise condition, where participants showed the same average stuttering frequency of 10% disfluencies was seen in baseline. This may be attributed to the absence of noise-cancelling headphones and/or 60 decibels of white noise, which could have diminished the effectiveness of the white noise in facilitating fluency (Garber & Martin, 1974).

## 5.6 Conclusion

We tested a novel application of choral speech as a potential tool for PWS to deliver presentations fluently. Results indicated that the choral speech method, in particular when PWS spoke in unison with computer-generated voices, led to a significant reduction in stuttering, by bringing it to near-absent levels. Additionally, a significant correlation showed that people who had more severe stuttering experienced a greater reduction in disfluent syllables and reading time. This approach offers a practical option for PWS to give stutter-free presentations. Future advancements in AI could further enhance the naturalness of computer-generated voices, making the choral speech experience more comfortable and aligned with the speaker's own voice. Furthermore, this method

could be integrated into exposure therapy, that can assist PWS to reduce anxiety related to public speaking.

# 6

# General Discussion

As mentioned in the introduction, stuttering is a prevalent communication disorder, affecting approximately 70 million individuals worldwide, across almost all cultures and languages (Van Riper, 1982). Its incidence rate significantly surpasses that of other speech disorders such as apraxia of speech, aphasia, and dystonia (National Institute on Deafness and Other Communication Disorders, 2024; Sommer et al., 2021; Yairi & Ambrose, 2013). Given its substantial impact, particularly in severe cases where disfluencies can disrupt up to 50% of spoken syllables and are accompanied by physical concomitants and affective disorders such as social anxiety (Blumgart et al., 2010; Iverach & Rapee, 2014), this thesis focuses on understanding the mechanisms underlying stuttering and developing potentially useful tools for people who stutter (PWS).

As presented in our results as well, one of the biggest challenges in understanding stuttering is the wide variation in how it appears, both between different people and within the same person over time (Constantino et al., 2016; Tichenor & Yaruss, 2021). Some people have severe disfluencies that make communication difficult, while others experience milder forms that have less impact. Even for the same person, stuttering can change depending on the situation, for example, whether they are speaking under a communicative pressure or not (Alm, 2004b; Caruso et al., 1994; Jackson et al., 2016, 2021; Sheehan et al., 1967). PWS do not stutter when talking to themselves when they are alone, but the stutter appears when they try to speak to someone else (Jackson et al., 2021). Understanding these differences requires a creative approach to both research and treatment; to fully address the unique ways stuttering affects each individual. Indeed, this heterogeneity makes it challenging to pinpoint a reliable neural correlate.

Meta-analyses have aimed to identify consistent neural signatures, but their findings diverge. Brown and colleagues (2005) reported overactivation in the right anterior insula and frontal operculum, reduced auditory cortex activity, and increased cerebellar vermis activation. Later meta-analyses offered mixed results: Budde and colleagues (2014) found increased activity in right insula and supplementary motor area (SMA) but failed to replicate the cerebellar findings. Belyk and colleagues (2017) also noted variations, identifying increased activity in the right Rolandic operculum and decreased activity in the left motor cortex. These inconsistencies may reflect the methodological differences between studies and also heterogeneity in stuttering within and between individuals.

Overactivation in the right inferior frontal cortex, particularly in the right frontal operculum and anterior insula, has been frequently observed in PWS during speech production tasks (Watkins et al., 2008; Neef et al., 2018). Other studies have also shown that this right hemisphere overactivity 'normalises' following speech therapy, resulting in more typical left-lateralised brain activity patterns (Kell et al., 2009; De Nil et al., 2003; Neumann et al., 2005). As discussed in chapter 3, these observations provided some support for the incomplete cerebral dominance theory, which suggests that competition between the brain's hemispheres for control of language and motor functions can lead to altered lateralisation in PWS (Orton, 1927; Travis, 1978). According to this theory, PWS tend to display greater rightwards lateralisation compared with controls during speech production.

In this thesis, we first investigated differences in brain activity between PWS and controls, using a relatively large sample by pooling data from four fMRI studies that employed a consistent methodological approach. Next, we revisited the incomplete cerebral dominance theory by investigating whether there were functional lateralisation differences in speech and language tasks between PWS and controls, by performing a direct statistical comparison between the two hemispheres. The second part of my thesis focused on methods that could potentially benefit PWS. In this context, we evaluated the effectiveness of theta-gamma-peak (TGP) transcranial alternating current stimulation (tACS) to enhance sensorimotor learning during speech

production. Finally, we explored the practical application of choral speech as a fluency-enhancing tool, evaluating whether the use of self-recorded speech or computer-generated speech as a second voice could help eliminate stuttering during presentations.

## 6.1 Overview of findings and contributions

In our initial study investigating brain activity differences between PWS and controls, the analysis using a strict statistical threshold corrected for multiple comparisons failed to identify any significant differences in blood oxygenation level-dependent responses between the two groups. In order to minimise the risk of overlooking subtle effects, we re-analysed the data using a more lenient, uncorrected threshold. At this level, we observed results consistent with earlier meta-analyses on stuttering, specifically reporting increased activity in the right insular cortex in PWS, which is a region previously identified as a neural marker of stuttering (Brown et al., 2005). However, no significant differences were found in the cerebellum or superior posterior temporal lobes, areas also suggested to be relevant in stuttering by Brown and colleagues (2005). In contrast to the findings of Budde and colleagues (2014), who reported reduced activity in the left red nucleus, our study revealed bilateral overactivity in this region in PWS. We interpreted this symmetrical overactivation in both red nuclei as a likely robust result rather than a false positive, possibly indicating a compensatory mechanism for the differences in the initiation circuit (Alm, 2004a; Chang & Guenther, 2020; Civier et al., 2013). Furthermore, we identified increased responses in the right anterior frontal cortex and decreased activation in the left superior frontal sulcus, as well as reduced activity in the inferior parietal cortex bilaterally. These patterns may reflect disruptions in the sensory feedback integration in PWS (Civier et al., 2010; Max et al., 2004), as discussed in detail in Chapter 2.

Our study contributes to the understanding of the neural correlates of stuttering, however, since our results were not statistically corrected despite the large sample size, our findings also highlight the need for further research to clarify these results using more ecologically valid task designs

(e.g., tasks with high communicative intent) to achieve statistically robust evidence and inform the development of targeted interventions for stuttering.

In the second study, we aimed to see if there were differences in language lateralisation between PWS and fluent speakers by analysing brain activity in areas related to language, namely the frontal and temporal lobes. We also looked closely at two regions in the inferior frontal gyrus, known as the pars opercularis (BA44) and pars triangularis (BA45), which play roles in higher language processing. Our main findings showed two things: first, there was no evidence to suggest that PWS have different language lateralisation compared with fluent speakers; instead, we found some support for the idea that they are similarly lateralised. Second, we noticed that leftwards language lateralisation was more robust during imagined speech tasks than during overt spoken tasks, and this was true for both groups. These results help fill a gap in the literature where previous studies observed more activity in the right hemisphere in PWS during speech but did not directly compare the two hemispheres. Overall, by directly testing the brain's activity on both hemispheres using a threshold-free bootstrap algorithm, we challenged the idea of altered hemispheric specialisation in stuttering. Fine-tuning these theories is essential for asking the right questions to understand the root causes of stuttering.

In our brain stimulation study, we administered TGP tACS over the articulatory representation in the left M1 to investigate whether this would enhance the expected adaptation response to an upwards shift in formant 1 (F1) frequency during auditory feedback. During the learning phase, both the TGP tACS and sham groups adjusted their speech by reducing their F1 values, and increasing their F2 values from the baseline. Contrary to our hypothesis, no significant differences were observed between the groups in their adaptation to the F1 shift by the end of the 30 learning trials or during the first 15 trials of the after-effect phase. However, when we expanded our analysis to include all 90 trials in the after-effect phase, a difference emerged: the mean F1 value for the TGP tACS group was significantly lower than that of the sham group. This finding suggests that TGP tACS may contribute to the durability of sensorimotor learning in speech. Moreover, the role of theta-gamma activity might play a role in reinforcing this learning.

Although these results are promising, they are still preliminary with one outlier found in the dataset, and further research is needed to confirm their validity and better understand the impact of TGP tACS on speech motor learning.

In our final study, we explored a novel use of choral speech during a presentation setting, which significantly reduced the mean stuttering rate from 10% in the baseline condition to below 3%, a level typically considered clinically fluent (Gordon & Luper, 1992). The data revealed that the severity of stuttering played an important role in how effective the choral speech technique was, especially when a computer-generated voice was used; participants with more severe stuttering experienced significant improvements in fluency and shorter reading durations. Those with higher stuttering severity also expressed a clear preference for using this method in future public speaking scenarios. One remarkable case involved a participant who reduced their disfluency from 49% to just 2% and cut their reading time from approximately 19 minutes to 4 minutes using the technique. Importantly, no noticeable differences in perceived speech naturalness were observed between conditions, suggesting that this method can enhance fluency while maintaining the natural rhythm and tone of speech. These results suggest that this method could be an effective tool for those with severe stuttering, and provide an option to deliver presentations, lectures, or even speeches at special events stutter-free.

Overall, my studies contribute to the literature by advancing our understanding of the neural correlates of stuttering, providing both direct and indirect evidence of differences in the sensorimotor integration and initiation circuits of speech in PWS. Additionally, I investigated potential tools aimed at supporting PWS who seek to improve their fluency in real life settings without sacrificing speech naturalness. The inconsistent findings in the literature regarding neural correlates underscore the importance of more ecologically valid task designs that address both neural and psychological aspects, as stuttering is a complex phenomenon (e.g., Jackson et al., 2021).

In the following section, I will propose a unified theory of stuttering to explain the variability seen within and between PWS. For example, in our data, one participant's stuttering rate decreased from 13% to 2% in the recording-alone condition, even when aware that the recording would be sent to the researcher. In contrast, another participant's disfluency increased from 1% to 7%. I believe this variability is worth to be discussed further. In the final section, I will outline future research projects that align with our findings and this theory, aimed at understanding the neural correlates of stuttering better, and improving speech fluency and reducing social anxiety in PWS.

## 6.2 A unified model of stuttering: threat conditioning modulates the sensorimotor integration and initiation circuit

Previous chapters have highlighted the dual role of neural mechanisms in stuttering, which involves differences in both sensorimotor integration and initiation circuits. For example, PWS can temporarily eliminate stuttering using techniques like choral speech (Saltuklaroglu et al., 2009; Virginia, 1939), which bypass disruptions in the sensorimotor system, or metronome-paced speech (Fransella & Beech, 1965; Howell & El-Yaniv, 1987), which directly addresses issues in the initiation circuit. However, stuttering does not emerge when PWS speak privately when alone (Jackson et al., 2021), suggesting the need for an additional component to explain the whole picture.

I propose that the variability in stuttering, both between and within individuals, may be significantly influenced by threat conditioning. This concept aligns with the earlier suggestion by Peters and Guitar (1991), who theorised that the freezing response could suppress vocal output. Expanding on this idea, I will explore how threat conditioning might modulate the neural circuits involved in stuttering, drawing upon evidence from both behavioural and neurobiological studies. Specifically, I will consider how threat-related signals could influence the sensorimotor integration system and initiation circuits, potentially playing a role in the emergence of stuttering as the third component.

Adopting an evolutionary perspective can provide valuable insights into developing theories for complex phenomena like stuttering. As mentioned in the introduction, the ability to speak fluently and in a manner that aligns with societal norms may be rooted in an evolutionary drive to avoid neglect or rejection by social groups, where exclusion could pose a serious threat to one's survival (Lieberman, 2013). To understand this further, it is important to mention how threat conditioning occurs and how organisms learn to avoid potential dangers.

Over millions of years, evolution has equipped living beings with the capacity to recognise and respond to predictive cues in their environment in order to enhance their chances of survival (Nasser & Delamater, 2016). For example, if a foraging animal associates the sudden movement of a branch with the presence of a lurking lion, it can quickly react to avoid harm. This kind of learning, usually described through implicit associative processes (also known as Pavlovian conditioning), depends on the brain's ability to connect different events a coherent pattern (Pearce & Hall, 1980). With repeated experiences, these associations strengthen by forming neural pathways that trigger automatic responses (Nasser & Delamater, 2016). Freezing is so important because predators respond to movement so if you remain still the predator may get bored (or does not detect you) and do something else (LeDoux, 2015).

Research on threat conditioning has repeatedly demonstrated the brain's ability to respond to threats in a manner that is both implicit and automatic (LeDoux, 2015). For instance, in their classic study, Iwata and LeDoux (1988) trained rats to associate a specific auditory cue with an electric shock. This type of cued threat conditioning involves presenting the animal with a tone (conditioned stimulus or CS) followed by a footshock (unconditioned stimulus or US), causing the animal to express a freezing response when only the tone is presented. Once conditioned, the rats exhibited a pronounced freezing response upon hearing the tone, displaying typical signs of anticipatory threat such as hunched posture, and reduced movement (Iwata & LeDoux, 1988). In contrast, rats exposed to a random pattern of tones and shocks without forming an association showed no such response. During freezing, the rat's muscles are largely immobilised, except for slight head movements to scan the surroundings. This response is typically the first reaction to

danger, that gives time to assess the threat before taking action (LeDoux, 2015). If the danger escalates, the body may shift to a fight-or-flight state, mobilising motor functions and overriding inhibition for immediate survival (LeDoux, 2015). Therefore, life-threatening situations have a way of reshuffling the brain's priorities.

Anecdotal evidence reported that PWS experienced sudden fluency when their survival was on the line, like during the intense moments of combat in World War II (Bloodstein 2021). In these cases, the brain's need to act swiftly and decisively seemed to override the habitual freeze response (Alm, 2004b). This is no surprise if we consider how the brain's threat detection system is wired to recalibrate on the fly. Within the stuttering community, it has been known that heightened states of rage, like the raw intensity of discussing a lost game or other charged moments, can break through the usual barriers to fluent speech (Reddit.com, 2020).

In Pavlovian conditioning, the strength of the unconditioned stimulus is a pivotal factor in shaping the threat response. Early research on the intensity of the CS and the conditioned response, demonstrated that the more intense the foot shock, the stronger the conditioned threat response in rats (Annau & Kamin, 1961). Moreover, in humans, prolonged exposure to the threat of shock results in a stable increase in anxiety (Cooper et al., 2022). This heightened state of anxiety of threat reflects sustained shift in brain activity patterns, locking the individual into a state of readiness for danger. Translating this to stuttering, it helps explain why PWS may develop a deeply ingrained freeze response in generalised social situations. Repeated negative social and self-evaluations of their disfluent speech likely act as potent unconditioned stimuli, conditioning the brain to perceive these social interactions as threats. Over time, this conditioning entrenches the freeze response, may make it a habitual reaction whenever these social triggers are present. These implicitly learned threat responses can indeed be different for each individual, which might be an explanation for the differences in stuttering levels to recording voice when PWS were alone. Yet, this is just one layer of the complexity. The variability in stuttering severity among individuals also depends on underlying differences in brain structure (Chang et al., 2008; Cykowski et al., 2010; Kell et al., 2009; Sommer et al., 2002; Watkins et al., 2008; see Neef et

al., 2015 for a review), and neural activity (Belyk et al., 2017; S. Brown et al., 2005; Budde et al., 2014) as discussed in previous chapters, suggesting that both learned responses and inherent biological factors intertwine to shape the within and between individual differences.

The relationship between bradycardia and exposure to threatening stimuli is worth to discuss (see Alm, 2004 for a detailed discussion). Bradycardia typically arises from increased parasympathetic activity (vagal activation) which counteracts the heart rate acceleration driven by sympathetic activation. While the sympathetic nervous system primes the body for fight-or-flight, the parasympathetic system triggers a freeze response (Mobbs et al., 2009). One study reported this interplay in cats, which responded to an approaching aggressive cat by freezing and exhibiting bradycardia, indicating a dominance of the parasympathetic response even amidst the heightened state of alert (Mancia et al., 1972). In humans, similar findings were reported, where both people with anxiety disorder and controls showed a reduction in heart rate during the anticipation of a shock (Santibáñez-H. & Schroeder, 1988). These findings suggest that a freeze response is marked by reduced heart rate and movement.

When considering stuttering, this physiological pattern appears relevant. PWS show reduced heart rate during speech tasks compared with fluent speakers, despite similar levels of sympathetic activation (Alm, 2004b). This suggests that, even in high-stress scenarios, their bodies might default to a freeze response rather than the typical fight-or-flight reaction. Supporting this, Caruso and colleagues (1994) found that under high-stress conditions, PWS had significantly reduced heart rates and increased disfluencies compared with controls. A recent study supported this finding by showing elevated parasympathetic activity during speech in socially stressful situations compared with controls, coupled with elevated self-reported anxiety among PWS (Bauerly et al., 2019). While their skin conductance, disfluency rates and heart rates remained consistent across conditions, participants showed different acoustic patterns in F2 frequency. It is important to interpret these findings with the understanding that PWS may be hypersensitive to any context involving communicative intent, which already primes them for a threat response. For instance, in the study of Bauerly and colleagues (2019), even the low-stress task, where participants

described their dream job, triggered disfluencies in PWS, suggesting that the baseline level of stress might already reach a ceiling due to the communicative intent. Even pseudo-word reading can involve communicative intent for some PWS, where the judgment of speech fluency carries informational value that is intended to be transferred to another agent. Nevertheless, the persistence of these parasympathetic response in PWS during the high-stress conditions and reduced hearth rate reported in the previous study (Caruso et al., 1994) might indicate a freezing mechanism, similar to those adaptive responses seen in both animal and human models of conditioned threat.

The concept of freezing is not a rigid, all-or-nothing state (Alm, 2004b). Instead, it operates along a spectrum, ranging from total immobility to partial inhibition of movement (Marks, 1987). This variability in the degree of freezing suggests that even when an organism appears still, it might not be entirely motionless but instead be selectively restricting certain movements (Alm, 2004b). When discussing freezing in the context of human behaviour then, especially in stuttering, this does not necessarily mean the individual is completely immobilised. One qualitative research suggested that gestures tied to speech are co-produced with fluent speech but tend to halt during disfluent episodes (Mayberry & Jaques, 2000). However, this suppression in gestures appears to be highly specific; while speech-related gestures freeze, other motor actions, such as drawing or tapping, can still occur during a disfluent moment. This selective inhibition in gestures implies that freezing is tied to communicative intent in stuttering, linked to the source of the threat.

Further speculation would be that the brain selectively inhibits motor activities directly involved in communicative intent as part of a defensive strategy to avoid any risk of stuttering moment which is likely to be associated with shame, guilt and fear. Drawing a parallel to animal models, when rats encounter a predator, they freeze to minimise visible movement, which reduces their chances of being detected. Yet, they may continue to produce ultrasonic vocalisations (also known as alarm cries) that fall outside the predator's hearing range (Parsana et al., 2012), specifying that the freeze response targets only those actions that would increase vulnerability to danger. Speculatively, in stuttering, this might correspond to the suppression of speech-related motor

activities, which a neural mechanism aimed at mitigating the perceived social threat while allowing non-communication related motor functions to continue (such as drawing out of communicative intent). This nuanced approach to freezing, both in animals and in humans, can shed light to why PWS do not stutter in self-directed speech, as there is no threat, thereby freezing related to communicative intent (e.g., Jackson et al., 2021).

Threat conditioning is a type of associative learning that operates below the level of conscious awareness (LeDoux, 2015). Unlike declarative learning, it does not necessarily result in a direct experience of fear or anxiety (Dolan & Vuilleumier, 2003; Phelps, 2006; see also LeDoux & Pine, 2016 for review). Research has shown that subliminal threats, presented below the level of conscious perception, can elevate amygdala activity and provoke peripheral responses, even without participants experiencing any conscious feelings of fear (Dolan & Vuilleumier, 2003; LeDoux & Pine, 2016). Moreover, people with "blindsight", who cannot consciously perceive stimuli in their blind field due to damage to a portion of the visual cortex, still show amygdala activation and defensive reactions when faced with threatening stimuli, without any conscious feelings of fear (Morris et al., 2001). This illustrates that the brain's circuits for processing threats can operate on a non-conscious level. In a similar way, PWS may display physiological reactions causing freeze response associated with communicative intent even in the absence of felt anxiety or fear, such as during conversations with family or close friends. These responses may be automatic and tied to the non-declarative learning of negative associations of communicative intent. Thus, while conscious thoughts about stuttering might interact with these implicit threat mechanisms, it is important to think of them as separate processes to fully understand their impact on articulation.

The most compelling evidence into the brain's inhibitory mechanisms that precede stuttering utterances has come from a recent MEG study (Orpella et al., 2024). The study revealed a surge in beta power within the right pre-supplementary motor area (R-preSMA) just before stuttered utterances. This heightened beta activity not only predicted the likelihood of a stuttering event but also correlated with increased stuttering severity and delayed speech onset. The response of R-

preSMA to stuttered speech is characteristic of its rapid, automatic reaction to inhibitory cues (Hannah & Aron, 2021). Similar neural patterns were observed in tasks like go/no-go paradigms, where actions must be abruptly halted in response to no-go signals (Aron, 2011). In this context, the threat conditioning may act as an implicit "stop" signal, picked up by MEG as increased beta activity. The authors also highlighted that these findings align with broader theories that suggest hyperactive inhibitory control within the right hemisphere's basal ganglia-thalamo-cortical loops, which play a critical role in the initiation circuit (Korzeczek et al., 2022; Neef et al., 2016, 2018).

In line with the research on threat conditioning and its neural underpinnings, both human and animal studies have established the pivotal role of amygdala in learning and retaining conditioned threat responses (Phelps, 2006). Recent findings extended this framework to stuttering by revealing neurophysiological links between amygdala and stuttering (Toyomura et al., 2018; Yang et al., 2017). For instance, Yang and colleagues (2017) showed that PWS increased connectivity in regions integral to the threat response, such as the right amygdala, prefrontal cortex, and insula, during speech tasks. Furthermore, Toyomura et al. (2018) found that elevated right amygdala activation in PWS was directly correlated with disfluencies during live interpersonal communication, which potentially situates the amygdala not only as a center of threat response but also as a modulator of speech fluency. These observations are the first attempts to build a potential bridge between the psychological and neural correlates of stuttering.

Theys and colleagues (2024) reported that the left amygdalostriatal area acts as a key network in stuttering, which seems in contrast to the involvement of the right amygdala showed in fMRI studies mentioned above. Through the analysis of three independent datasets, including two acquired neurogenic and one persistent developmental stuttering, the authors showed a consistent neural network centered around the left putamen, claustrum, and amygdalostriatal transition area (Theys et al., 2024). The positioning of this region between the posteroventral putamen and amygdala is thought to suit it for integrating threat evaluation with motor output, which could be essential for both adaptive and maladaptive responses (Theys et al., 2024).

One animal study examined the impact of selective lesions in different regions of the striatum on cued threat conditioning in rats, and reported that only lesions to the ventral striatum significantly reduced freezing behaviour during training and recall phases (Wendler et al., 2014). However, since freezing was assessed throughout the entire recall session, rather than specifically during the cue, it is challenging to distinguish whether the freezing response was contextually driven or cue-specific. This nuanced finding may have parallels with the continuous freezing response of speech observed in PWS during social interactions or recordings, suggesting that the threat response can persist across the entire duration of learned threat.

While the study of Theys and colleagues (2024) suggests a neural network hub for understanding stuttering, questions remain about the fluency effect of private speech for people with acquired stuttering, which is well-documented in developmental stuttering (Jackson et al., 2021) but yet to be explored in acquired cases. Further exploration into the phenomenon of private speech in people with acquired stuttering could yield critical information into whether developmental factors are essential for the process of threat conditioning to influence sensorimotor integration and initiation circuits.

Building on behavioural and neurobiological evidence, the theory that threat conditioning modulates the sensory-motor integration system and initiation circuit in PWS opens new avenues for understanding the core mechanisms underlying stuttering together with the fluency enhancers. The freeze response, an implicit defensive reaction linked to threat detection, could be at the heart of the speech interruptions observed in stuttering (Peters and Guitar, 1991). This interference likely disrupts the sensory-motor integration process essential for reading articulatory motor commands from memory without relying on auditory feedback (Civier et al., 2010; Max et al., 2004; Max & Daliri, 2019) or impairs the initiation circuits of these motor commands (Alm, 2004a; Chang & Guenther, 2020; Civier et al., 2013) or affecting both of the systems.

This account posits that threat conditioning in stuttering emerges over years of repeated social and self-evaluative negative feedback associated with disfluent speech. For example, a child may

begin with a subtle disfluency, such as whole-word repetition, which initially might be inconsequential. However, if that child encounters frequent negative reactions from family, peers, or educators whether these are overt judgments, expressions of frustration, or subtle signs of neglect the brain starts to tag these disfluent moments as threats (Guitar, 2019). Over time, this conditioning process transforms into an automatic response where stuttering cues trigger the same neural circuits involved in threat detection. This reaction selectively applies to the speech-motor functions, creating a form of habituated freeze response deeply embedded for over the selection, sequencing and initiating articulatory motor commands.

The notion that PWS develop a conditioned threat response specifically tied to communicative acts suggests that higher-order conditioning extends beyond stuttering moments, that affects fluency in broader contexts in which speaking occurs (Alm, 2014; Hahn, 1940; Jackson et al., 2016; Jon & Esther, 1945; Perkins William; Kent Raymond; Curlee Richard, 1991; Peters & Guitar, 1991; Quarrington, 1965; Sheehan et al., 1967; Smith & Weber, 2017). Over time, this threat response activates in almost any setting involving communicative intent interfering with the sensory-motor integration system and initiation circuit, however certain interventions can bypass these disruptions: for example, altered auditory feedback or choral speech (Adams & Hutchinson, 1974; Altrows & Bryden, 1977; Kalinowski & Saltuklaroglu, 2003; Peter Howell, 2004; Saltuklaroglu et al., 2009) can help circumvent issues in sensory-motor integration, while metronome-paced speech (Fransella & Beech, 1965; Howell & El-Yaniv, 1987) can aid in overcoming initiation failures. From the threat conditioning aspect, intense emotional states, like rage (which shifts the body into a fight-or-flight mode from freeze) (Brundage et al 2021), and self-directed speech (where the threat of communicative intent is absent) (Jackson et al., 2021) may suspend the freeze response, and facilitate fluent speech.

## 6.3 Suggestions for future research

Further research is warranted to explore the temporal and spatial interactions between the threat response, sensory-motor integration, and initiation circuit. The use of neuroimaging methods with

high temporal resolution like MEG to identify differences in brain function preceding stuttered utterances could be critical in clarifying the neural correlates underlying this complex interplay (Orpella et al., 2024). Moreover, data from implanted electrodes in patients with epilepsy who also have developmental stuttering could provide gold standard data with high temporal resolution, particularly through single-neuron recordings from regions such as the amygdala, cortico-basal ganglia-thalamocortical loop, including the pre-SMA and fronto-temporal areas.

Despite extensive research, no definitive treatment for stuttering has been established yet. One study showed that the application of transcranial direct current stimulation (tDCS) over left inferior frontal cortex improves speech fluency in adults who stutter (Chesters et al., 2018), which also normalised the brain activity in the cortico-basal ganglia-thalamocortical loop connected SMA (Chesters et al., 2021). The fluency improvement after therapy was maintained during reading but not during conversation, suggesting that both the neural and psychological aspects of stuttering needs to be addressed.

Here, I propose The BraveVoice Stuttering Treatment Protocol, designed to enhance speech motor control by integrating fluency training with TGP tACS or another non-invasive brain stimulation technique such as monophasic intermittent theta-burst stimulation, a form of transcranial magnetic stimulation (TMS) (Wendt et al., 2023), within immersive virtual reality (VR) environments. This combined approach emphasises the ecological validity of fluency intervention by enhancing motor learning of fluent speech in situations with high speech demands, while providing a safe environment to create positive speech memories.

VR could be a useful tool for stuttering as PWS with social anxiety disorder often avoid social interactions and might hesitate to pursue treatments that involve exposure to social situations. The use of immersive technologies like VR would also be helpful to expand access to effective treatment for PWS by facilitating immersive speaking experiences that simulate real-life interactions. Thus far, VR has been successfully utilised in treatment of various anxiety disorders (Bouchard et al., 2017; Freeman et al., 2018, 2022). For instance, research involving VR with

people struggling to leave their homes because of anxiety reported significant decreases in both the avoidance of, and distress in, daily situations when compared with standard care (Freeman et al., 2022). In particular, the more severe the anxiety and avoidance behaviours were, the more pronounced the benefits of the treatment. This VR program has become accessible to patients via the NHS. Another study showed that an automated psychological treatment delivered through VR was successful in diminishing fear of heights (Freeman et al., 2018). Assuming that the fear of heights can be triggered through threat conditioning, VR has the potential to show promising results for PWS in unlearning the threat association with communicative intent in real-life scenarios. In consistent with these findings, another study found that combining VR with cognitive behavioural therapy for social anxiety disorder was more effective and practical for therapists than traditional in vivo exposure, showing significant improvements in treatment outcomes that were maintained at the 6-month follow-up (Bouchard et al., 2017).

Considering the importance of the psychological aspect of stuttering, there have only been a small number of studies investigated the usage of VR with PWS (Chard & van Zalk, 2022). A study using VR exposure therapy with five participants revealed that VR effectively mimicked stress-inducing scenarios (Vona et al., 2023). Another study involving ten children and adolescents who stutter, found similar findings by showing that self-reported anxiety levels and stuttering severity did not differ when speaking in front of a virtual class compared with a real audience (Brundage & Hancock, 2015). A similar study involving 10 adults who stutter found that while stuttering frequency and physiological responses (skin conductance level and heart rate) remained consistent across virtual speaking conditions, subjective distress levels were significantly higher when addressing a virtual audience compared with speaking in a virtual empty room (Brundage et al., 2016). These findings suggest that VR could serve as an effective tool for practicing fluency treatment in a safe, controlled, and automated way. However, to my knowledge, no research has utilised VR to develop a speech fluency therapy in various social settings simulating the real-life complexity.

The effectiveness of combining non-invasive brain stimulation and VR in rehabilitation has been explored in various therapeutic applications such as stroke, neuropathic pain, cerebral palsy, phobia, post-traumatic stress disorder, and multiple sclerosis rehabilitation (Cassani et al., 2020). A meta-analysis analysed the efficacy of integrating brain stimulation with task practice in VR environments to enhance upper limb motor improvement in stroke patients (Subramanian & Prasanna, 2018). Preliminary evidence from five studies indicates that this dual approach is effective during the subacute phase of stroke. A more recent meta-analyses added that the combined therapy offers a more effective rehabilitation strategy, enhancing the quality of life for patients recovering from stroke (Meng et al., 2023). To my knowledge, the combined use of VR and brain stimulation to improve speech fluency and reduce social anxiety in PWS has not been previously studied.

In conclusion, The BraveVoice Treatment Protocol aims to build upon prior work that successfully enhanced speech fluency in reading condition but not in conversation using tDCS (Chesters et al., 2018). I hypothesise that people undergoing speech fluency treatment in VR (addressing psychological correlates), while receiving stimulation targeting the feedforward controller (addressing neural correlates) will exhibit improved speech fluency compared with those receiving a sham treatment. Additionally, my secondary hypothesis focuses on diminishing social anxiety among PWS, following the VR-based immersive therapy. The main goal of this research is to develop a reliable therapeutic option for stuttering that can be reached through the NHS. I am actively pursuing funding opportunities to bring this research and many other ideas to life at the earliest convenience.

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