NEUROMAGNETIC BETA BAND ABNORMALITIES IN STUTTERING DURING THE PERCEPTION AND PRODUCTION OF RHYTHM

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Declaration of Originality

I certify that the work in this thesis entitled "Neuromagnetic beta band abnormalities in stuttering during the perception and production of rhythm" has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university, or institution than Macquarie University.

I also certify that the thesis is an original piece of research and that it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself has been appropriately acknowledged

In addition, I certify that all information sources and literature used are indicated in the thesis.

The research presented in this thesis was approved by Macquarie University Ethics Review Committee, reference number:

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Abstract

Recent work provides evidence that stuttering can be considered a disorder of timing. A separate body of literature suggests that the neural oscillations within the canonical beta band (12-30Hz) are important for timing and rhythm. The present thesis aimed to link these two areas of research by using magnetoencephalography (MEG) to examine beta band responses to the perception and production of rhythm in adults and children who stutter (AWS and CWS respectively).

I first review the neurological substrates associated with normal speech production in order to build a foundation for understanding impaired speech production. Secondly, I review the past ten years of neuroimaging research on developmental stuttering to gain an overall state of the literature and discuss the need to focus research on CWS. Thirdly, I present multimodal neuroimaging evidence for the view that the core deficit in developmental stuttering is a disorder of timing. Fourthly, I detail the role of the beta band in timing and rhythm as it applies to stuttering. The experimental chapters then follow.

The first experiment used MEG in conjunction with dynamic causal modelling (DCM) to measure the effective connectivity between the auditory and motor cortices in the beta band during synchronised and syncopated finger tapping in AWDS. The second experiment aimed find differences in neuromagnetic beta band activity between AWS and AWDS when they are engaged in paced and unpaced finger tapping. The third experiment aimed to assess the feasibility of recording beta band activity from children who do not stutter (CWDS) when listening to trains of rhythmic sounds (390ms, 585ms and 780ms) in order to later assess this in CWS. The fourth

and final experiment compared beta band responses of CWS and CWDS while passively listening to either a rhythmic (450ms) or less rhythmic trains of sounds (SOA varying between 300 and 600ms).

The results of the first experiment in AWDS showed that both synchronisation and syncopation tapping was driven by auditory feedback in the beta band as evidenced by the winning model containing connections propagating from the auditory to the motor cortex. It also revealed that the difference between synchronisation and syncopated tapping was best explained by connections going from the motor cortex to the auditory cortex and vice versa suggesting that it placed greater demands on motor activity. The second experiment established that AWS exhibit greater beta band modulation compared to AWDS during synchronised but not syncopated finger tapping in the left motor cortex. The third experiment established that CWDS tolerated listening to repetitive trains of sound for a period of about 30 minutes relatively well. It also showed that CWDS exhibit a beta band (12-15Hz) response similar to what has previously been observed in adults. The fourth and final experiment confirmed these results in another sample of CWDS. Interestingly, however, the CWS compared to CWDS in this study showed a beta band response between 12-15Hz that was out of phase with the beta band response of CWDS. Overall, I show that AWS and CWS exhibit abnormalities in the beta band and build upon the idea that stuttering is related to deficits in timing.

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Abbreviations

AWS = Adults who stutter

AWDS = Adults who do not stutter

BMS = Bayesian Model Selection

CWS = Children who stutter

CWDS = Children who do not stutter

DCM = Dynamic Causal Modelling

DIVA = Directions into Velocity of Articulators

DTI = Diffusion Tensor Imaging

EEG = Electroencephalography

ETN = External Timing Network

FDR = False-discovery Rate

fMRI = Functional Magnetic Resonance Imaging

GODIVA = Gradient Ordered Directions into Velocity of Articulators

HSFC = Hierarchical State Feedback Control

ITN = Internal Timing Network

MAD = Mean Absolute Deviation

MEG = Magnetoencephalography

MEP = Motor Evoked Potential

MMN = Mismatch Negativity

MNI = Montreal Neurological Institute

MRI = Magnetic Resonance Imaging

NIRS = Near Infra Red Spectroscopy

PET = Positron Emission Tomography

PMC = Premotor Cortex

PWDS = People Who Don't Stutter

PWS = People Who Stutter

RMS = Root Mean Square

SFC = State Feedback Control

SMA = Supplementary Motor Area

SNIZE = synchronise

SOA = Stimulus Onset Asynchrony

SPATE = Syncopate

TES = Transcranial Electric Stimulation

TMS = Transcranial Magnetic Stimulation

Chapter 1

General Introduction

1.1 Introduction

A story recounted by a famous Australian musician goes like this, "One of the worst things that can happen to me is to meet a person who stutters. When they introduce themselves, saying, 'M-m-m-m-m my name is Jon' my reply is, 'M-m-m-m-m my name is Meg'". This isn't because she is mocking them or making fun of them, but rather because she also has a stutter. Meg goes on to say that people often think she is drunk, drugged or has forgotten their names. Meg reveals these things because, at heart, she is an artist, a singer and a songwriter - and that is built on a platform of honesty. For her, singing is more than making nice sounds and more than feeling known or understood. For Meg, singing is sweet relief and is the only time when she feels fluent. She ponders, with a sparkle in her eye, 'somehow through some miraculous synaptic function of the human brain, it is impossible to stutter when you sing. The average adult produces up to 16,000, words per day (Mehl et al.,

2007); the frequency and ease with which we speak hides the fact that it is incredibly complex. Yet most of us do it without a second thought. But imagine what it would be like to know exactly what you want to say, but struggle to make the movements to say those words. People who stutter (PWS) do not have to imagine this or the situations described above because they face them every single day.

Stuttering is characterised by speech repetitions, prolongations and blocks (Riley, 1972) and affects tens of millions of people around the world. The disorder usually manifests between three and five years of age as a child is beginning to develop their spoken language skills. While it is estimated that up to 80% of children who stutter will spontaneously recover (Yairi and Ambrose, 1992), the remainder will continue to stutter into adulthood. Although negative side effects of stuttering are not generally observable in the first year after onset (Reilly et al., 2013), stuttering for an extended period of time can have significant impacts on quality of life and mental health (Boyle, 2015; Gunn et al., 2014; Iverach et al., 2009, 2010). Despite the investment of significant time and effort into stuttering research, the cause of the disorder remains unknown. While a number of treatments do exist, the reason for their effectiveness is not well understood. For example, recent work challenges the assumption of the Lidcombe Program (Harris et al., 2002) that the reduction in stuttering severity is attributable to a request for self-correction (Donaghy et al., 2015). While individual therapies are relatively effective (see for review Baxter et al., 2015), the reasons why are largely unknown. Current treatments are arguably stymied because they focus on the symptoms of the disorder rather than what is actually causing it. Stuttering is indeed a mystery. But what if the key to unlocking this mystery was some miraculous synaptic function of the human brain?

This dissertation and the work presented herein is motivated by 1) a large body of literature showing regions of the brain involved in speech production are also involved in the processing of rhythm (e.g. Alario et al., 2006; Fujii and Wan, 2014; Kotz and Schwartze, 2010; Price, 2010, 2012) and 2) that these regions exhibit structural and functional abnormalities in people who stutter. There are indeed widespread differences in the structure and function of cortical and subcortical regions involved in both timing and speech production in people who do and do not stutter (Etchell et al., 2014a). We can gain crucial insights into the brain basis of the disorder by considering the effects of conditions that alleviate or exacerbate stuttering. Such studies could provide the key to unlocking the mystery of stuttering. While singing uses the same articulatory musculature as speech and engages similar (though not identical) neural mechanisms (Özdemir et al., 2006), it places a much greater emphasis on rhythm (Alm 2004 and see also Gunji et al. 2007). Interestingly, recent work suggests that the benefits of singing in treating aphasia may in fact be attributable to rhythm (Stahl et al., 2011).

Some early behavioural studies provided interesting insights into stuttering. PWS speak fluently in the presence of a metronome even when they are not instructed to speak in time with it (Greenberg, 1970). Other authors have noted that a metronome produces a synchronisation effect whereby motor responses become timed or entrained to the beat (Azrin et al., 1968). The basal ganglia responds strongly to rhythmic stimulation (Grahn et al. 2007; Grahn and Rowe 2009; see for review Merchant et al. 2015). The level of activity in this area is typically reduced in AWS relative to adults who do not stutter (AWDS), but becomes normalised in the presence of a metronome (Toyomura et al. 2011 see also Toyomura et al. 2015).

The basal ganglia exhibit structural (Beal et al., 2013) and functional abnormalities in CWS (Chang and Zhu, 2013) which are thought to relate to deficits in the timing of self paced movements such as speech. The basal ganglia are involved in the timing and sequencing of speech (Alm, 2004; Civier et al., 2013; Fujii and Wan, 2014; Jin and Costa, 2015; Schirmer, 2004). Interestingly, the application of rhythm or timing to speech therapy seems to be one of the most effective forms of therapy especially among young CWS. Syllable timed speech reduces stuttering severity 55% and 80% in school aged CWS (Andrews et al., 2012) and strikingly, by 96% in most preschool aged CWS (Trajkovski et al., 2011). Perhaps rhythm-based treatments are so effective because they target the dysfunction at the heart of stuttering.

Behavioural studies show CWS are considerably worse than CWDS at producing rhythmic motor movements (Falk et al., 2015; Howell et al., 1997; Olander et al., 2010) and discriminating between auditory rhythms (Wieland et al., 2015). Additional evidence for the involvement of the basal ganglia in the onset of stuttering comes from the fact that damage to this region can sometimes result in stuttering (Tani and Sakai, 2011) and deficits in temporal processing (Schwartze et al., 2011). Indeed recent work also shows that patients with lesions to the basal ganglia have deficits in the ability to adapt to the temporal structure of not only simple rhythms, but also more complex signals like speech (Kotz and Schmidt-Kassow, 2015). Further, activity in the basal ganglia is positively correlated with stuttering severity (Giraud et al., 2008) and is predictive of recovery from stuttering after treatment (Ingham et al., 2013). Some authors have reported that dopamine antagonists reduce stuttering severity (Brady et al., 1991; Maguire et al., 2004). It has even been suggested that the stuttering-like dysfluencies observed in individuals with Parkin-

son's Disease are a direct result of dopaminergic medication (Tykalová et al., 2015). Notably, modulation of dopamine levels also influences temporal predictions (Coull et al., 2012; Mauk and Buonomano, 2004; Wiener et al., 2011); see for review Coull et al. 2011). Taken together, the neural overlap between stuttering and rhythm highlights the possibility that stuttering could indeed be a deficit in the timing of speech.

Most of the neuroimaging of stuttering to date has utilised cerebral bloodflow based techniques. Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI) have excellent spatial resolution owing to the fact that they measure changes in neural activity associated with changes in bloodflow. However, since blood takes several seconds to flow to a region of the brain once it has been activated, PET and MRI lack the temporal resolution to image the fast paced neural dynamics associated with the rhythm and timing of speech production. This is illustrated by considering that a person can speak up to 6 syllables in a second. The tools that are best suited to imaging the temporal dynamics of speech and timing are magnetoencephalography (MEG) and electoencephalography (EEG).

1.2 MEG

When a sufficiently large population of neurons receives synaptic input, they generate an electrical current which in turn produces a magnetic field. Magnetoencephalography (or MEG) uses an array of sensors positioned around the head to record small fluctuations in these magnetic fields (see Figure 11.1 for an example of sensory layout).

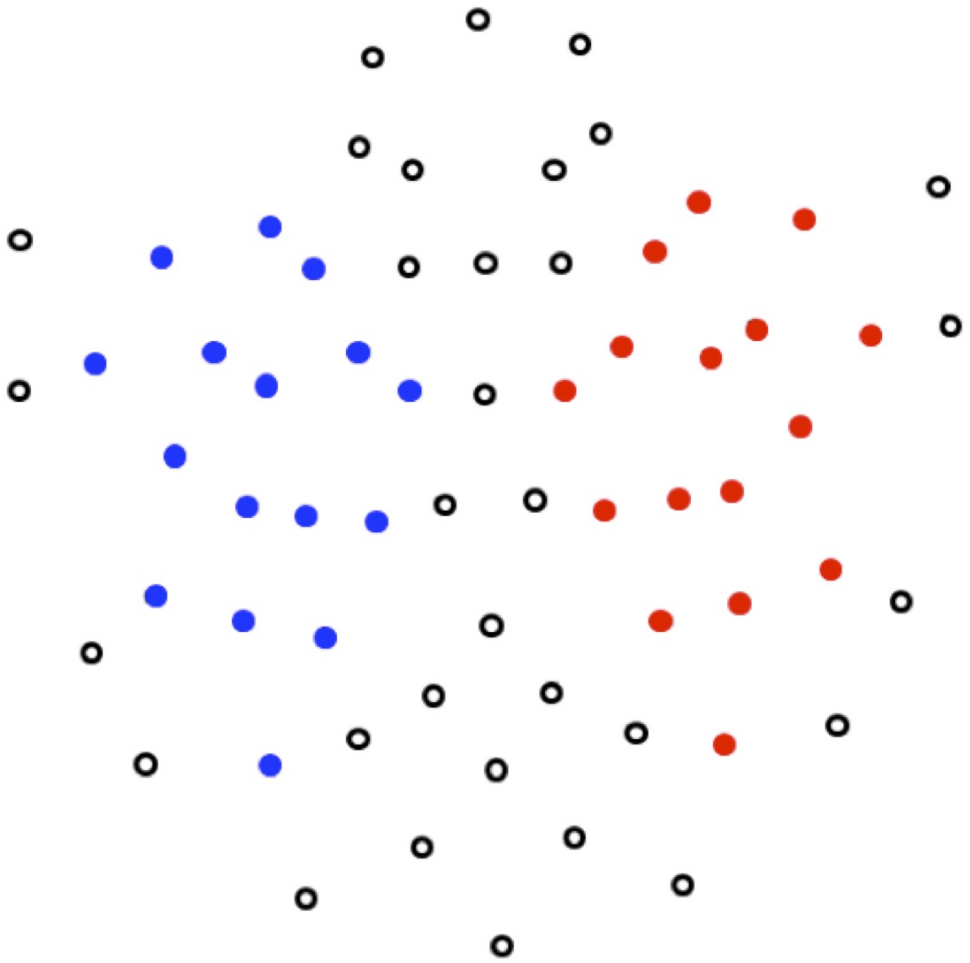

Figure 1.1: Example of a sensor array for the paediatric MEG system. The solid blue and red dots depict the 16 sensors representative of the auditory cortices in the left and right hemisphere respectively. The open black dots depict the remaining 32 sensors that were not analysed. The top of the image is anterior to the head and the bottom of the image is posterior to the head. Left is on the left and right is on the right.

The main advantage of MEG is that it has very high degree of temporal resolution because it is a direct measure of neural activity. Another advantage of MEG is that it has a better spatial resolution than EEG because magnetic fields are less distorted by the brain and surrounding tissue than electrical currents. Finally, MEG is a non-invasive neuroimaging technique and is therefore very safe. It does not emit fields or require the injection of isotopes, but only detects changes in neural

activity (Hansen et al., 2010).

Notably, the magnetic fields generated by the brain are very small (approximately 10 femtotesla). In order to be able to detect these very small signals, the sensors used to detect the signal - super conducting quantum interference devices (or SQUIDs) - must be super cooled using liquid helium (Hansen et al., 2010) which results in substantially increased operating costs. Because the signals emitted by the brain are several orders of magnitude weaker than those produced by traffic, mobile phone and other devices it is necessary to place the MEG system in a magnetically shielded room (or MSR). Before entering the MSR, participants are required to remove all metallic objects (such as belts, shoes, coins, keys, dental implants and mascara) and electronic devices (such as mobile phones) because failure to do so, though generally safe, can saturate the sensors potentially leading to the loss of data. Next, an elasticised cap containing five marker coils is then placed on their heads and fiducals (the nasion and the left preauricular points) are marked. This respectively allows researchers to calculate the extent of head movement in the MSR and coregistration with a template brain or MRI in later analysis for source localisation.

Further since magnetic fields decay with distance, MEG is most sensitive to activity generated by the cortex and less sensitive to activity generated by subcortical sources. Finally, due to the properties of magnetic fields, MEG is only able to detect activity in tangentially oriented neurons (in the sulci) Hansen et al. 2010).

1.3 Oscillations and MEG

These tools provide information not only about evoked responses, but also about neural oscillations. Neural oscillations are not simply epiphenomenal, but are also related to specific cognitive functions. For example, the beta band (12-30Hz) is typically related to motor activity. Beta power decreases when a person imagines, observes or executes a hand (Burianová et al., 2013) or mouth movements (Gunji et al. 2007; Jenson et al. 2014b,a; see also Toyomura et al. 2010). Beta oscillations can be recorded from several cortical and subcortical regions (Brittain and Brown, 2014; Brittain et al., 2014; Bartolo et al., 2014; Bartolo and Merchant, 2015; Jenkinson and Brown, 2011; te Woerd et al., 2014). A more recent finding is that neural oscillations in the beta band contribute to our ability to track rhythm (Arnal and Giraud, 2012; Fujioka et al., 2009, 2012; Giraud and Poeppel, 2012b; Merchant et al., 2015). For example, passive tracking of isochronous rhythms engages auditory motor regions of the brain in the beta band. Beta power peaks before the onset of the next expected stimulus in an isochronous sequence (Cirelli et al., 2014; Fujioka et al., 2012). Oscillations in the beta band are also associated with accuracy in predictive timing tasks (Arnal et al., 2014). Additionally, beta band activity can be modulated not just by perception of a rhythm, but by the expectation of a rhythm (Todorovic et al., 2015). Interestingly, beta band activity is impacted by levels of dopamine (for review see Jenkinson and Brown, 2011). Furthermore, beta oscillations have been linked to top-down control over sensory regions (Arnal and Giraud, 2012; Friston et al., 2015; Wang, 2010) and more directly to speech production (Arnal et al., 2011; Jenson et al., 2014b,a; Piai et al., 2015)

Neural oscillations have a putative role in some neuropsychological disorders such as schizophrenia, Parkinson's disease, Alzheimer's disease and autism (see for review Uhlhaas and Singer, 2006). The same may be true for stuttering. It is known that low levels of dopamine cause larger beta band power (Kononowicz and van Rijn, 2015). Conversely then, an excess of dopamine - such as in PWS (Wu et al., 1997) may result in atypical beta band modulation. This in turn may adversely affect the timing of self-paced movements characteristic of stuttering.

The main hypothesis to be investigated in this dissertation is that PWS have abnormalities in the phase of the envelope of beta oscillations in the brain networks that underpin the perception and production of time. These impairments are thought to relate to deficits in speech production that are characteristic of stuttering. The goal of this dissertation is to test this hypothesis in samples of adults and children who stutter and thereby contribute to our understanding of the neural basis of stuttering. Moreover, it is hoped that by gaining a better understanding of pathological brain mechanisms in stuttering, this series of studies will shed light on how these mechanisms work in the normal brain.

1.4 Paediatric Magnetoencephalography

In recent years, significant progress has been made regarding the brain basis of stuttering. The vast majority of research to date has been conducted on adults who stutter (AWS). This carries important implications for the interpretation of results from the aforementioned studies. In particular, it means researchers do not know whether differences between AWS and adults who do not stutter (AWDS) reflect

causal or compensatory mechanisms in stuttering because stuttering over a long period of time - like any activity - causes changes in the structure and function of the brain. For this reason, the neural responses observed in adults are very likely different from the neural responses observed in children. For example, whereas (Salmelin et al., 2000) found enhanced beta band power in the left hemisphere of AWS, (Özge et al., 2004) found reduced beta power in the left hemisphere of CWS. These inconsistencies do not invalidate the results of neuroimaging or neurophysiological studies in PWS but simply raise a question regarding the interpretation of differences between groups. An obvious answer to this conundrum would be to test children. However, in practise this is more challenging than it first appears. In part this is because many neuroimaging methods are generally unsuitable for children. It is not ethically justifiable for example to make invasive intracranial recordings in the basal ganglia of stuttering let alone healthy children. fMRI is particularly noisy and may not be well tolerated by younger children.The fixed sensor geometry of MEG can make it difficult to accurately measure signals from the brains of children (who have smaller heads than adults) because the magnetic fields MEG measures decay exponentially with distance. While EEG is more tolerable of movement, it has a poorer spatial resolution than MEG and can be time consuming and uncomfortable to set up. Fortunately, recent advancements in the field of neuroimaging has led the development of neuroimaging techniques that are specially designed for children. Accordingly, there has been a corresponding increase in the number of studies investigating brain activity in both typically developing and clinical groups of children (e.g. Chang and Zhu, 2013; Chang et al., 2015; Sowman et al., 2014; Sato et al., 2011). With respect to this dissertation, a custom built paediatric MEG affords the opportunity to com-

pare the cortical beta band activity of young CWS at a time close to the onset of the disorder, when they do not exhibit such widespread reorganisation of the brain as do AWS (Chang et al., 2008).

1.5 Organisation of the Dissertation

This dissertation is structured as follows: Chapter 2 provides an overview of the development of speech and associated neural substrates. Chapter 3 is a more detailed account of the auditory motor integration and the role of rhythm and prediction in speech production. Chapter 4 is a systematic review of the past twenty years of neuroimaging research. Chapter 5 outlines perceived difficulties in testing children in conjunction with neuroimaging techniques and offers some solutions to these problems. Chapter 6 reviews multimodal behavioural and neuroimaging evidence for a deficit in brain timing networks in developmental stuttering. Chapter 7 outlines more specifically the neural basis of stuttering and proposes that it is manifest in the dynamics of beta band oscillations in the human brain. Chapters 8-11 contain the main body of research. Chapter 8 details an experiment on healthy adults designed to test whether it is possible to detect beta band oscillations in a paced and unpaced finger tapping paradigm. Chapter 9 tests whether there are differences in neuromagnetic beta band oscillations between AWS and AWDS on a paced finger-tapping task. Chapter 10 describes an experiment-testing the feasibility of recording neuromagnetic beta band activity from CWDS in response to isochronous sounds at three different tempos and whether neural responses to changes in tempo are evident in these children. Chapter 11 reports a follow-up experiment comparing how CWS

differ from CWDS in beta band dynamics in response to a train of rhythmic and less rhythmic sounds. Chapter 12 concludes the dissertation. It integrates the results of the experimental chapters placing them in the context of the broader scientific literature, outlines limitations of the current studies and provides directions for future research.

Chapter 2

Speech Acquisition

To better understand impaired production, it is first necessary to have an understanding of how speech develops. This chapter outlines the milestones in developing speech and the corresponding neural changes that accompany them.

2.1 Introduction

The ability to speak is a truly remarkable feat. Adults for example, are capable of generating 2-3 words per second from a lexicon of well over ten thousand words (Levelt et al., 1999). Fluent speech is such a central part of our everyday communicative interactions that we do not often stop to think about how this process is achieved. Even the ostensibly simple act of saying a word like 'cat' is actually very complex. Indeed, the frequency and ease with which we speak belies the true nature of the task. Human speech requires the precise coordination of over 100 muscles in the larynx and pharynx, mouth, jaw and tongue and the respiratory system over a very fast timescale compared to that for limb movements. It imposes a high degree of constraint on movement that comes from the demands of phonology, syntax and the pragmatics of a language. It also requires the ability to successfully integrate auditory and motor information (Abbs et al., 1984; Ackermann and Riecker, 2004; Levelt et al., 1999). To properly understand this complex feat, it is necessary to discuss how speech production develops, the brain mechanisms behind fluent speech and the related computations that must be performed. Accordingly, this review aims to synthesise the current literature with a particular focus on the milestones of normal speech production and corresponding neurological changes.

The earliest neural models of speech production were formulated by observing the behavioural deficits that resulted from lesions to specific areas of the brain. Pierre-Paul Broca made a landmark discovery in the field of neuroscience when he found that damage to the left inferior frontal gyrus led to the arrest of speech but not impairments in comprehension (Broca, 1861). That is to say, he found that

Broca's area plays an important role in the motor control of speech (MacNeilage, 1998). Perhaps an equally ground-breaking discovery was that damage to the posterior section of the superior temporal gyrus, also known as Wernicke's area, led not to deficits in the production of speech, but rather deficits in the ability to comprehend spoken words (Wernicke, 1874). Such work revolutionised our understanding of speech processing by providing a convincing demonstration of compartmentalisation of brain function. Whereas Broca's area was specialised for the production of speech, Wernicke's area was specialised for the comprehension of speech. Ultimately, work by Broca, Wernicke, Lichtheim and their contemporaries led to the formulation of numerous neural models of speech production.

The classic neural model of speech production was developed jointly by Wernicke and Lichtheim. This theory held that in order to speak, the meanings of words are sent from Wernicke's area, via the arcuate fasciculus, to Brocas area. In this view, Broca's area was theorised to contain a means of articulating words. These were subsequently transmitted to the facial area of the motor cortex and then towards the facial motor neurons in the brainstem to command facial muscles. Although the Wernicke-Lichtheim model is now obsolete (Poeppel and Hickok, 2004; Poeppel et al., 2012), it served as a foundation influencing the development and refinement of more modern neurophysiological models of speech production. More specifically, the Wernicke-Lichtheim model introduced the idea that speech production depended on an interaction of both auditory and motor systems. The importance of the auditory and motor systems for speech production is most clear when examining the acquisition of speech. It should be noted that knowledge of normal brain maturation is crucial for understanding normal brain function in adults as well as neurodevel-

opmental disorders (Gogtay et al., 2004). In the following section I present a brief overview of normal developmental trajectory of speech production in infants and children.

2.2 Developing the ability to speak fluently

Speech production is not an innate ability per se, but rather one that is acquired and refined over a long period of time. This process goes hand in hand with brain maturation (Friederici et al., 2011; Johnson, 2001) and it is therefore important to examine how these neural changes relate to behavioural changes that occur as a child grows. Regardless of their culture, young children follow the same developmental trajectory to acquire fluent speech (Kuhl, 2004). This process begins before birth. Babies in the womb become sensitive to their native language around the third trimester (Sundara and Scutellaro, 2011). The cries of neonates (aged 2-5 days) are tuned to their native language. Whereas French newborns produce cries with a rising melody contour, German newborns produce cries with a falling melody contour each of which is characteristic of their native language (Mampe et al., 2009). This suggests that even such immature vocalisations are shaped by perception - in this case prenatal perception. Speech directed at two-day old infants activates brain regions known to be associated with speech production in adults, but unlike adults, tends to be right lateralized (Perani et al., 2011), which is thought to reflect a greater reliance on prosodic information in infants. Three day old infants are able to detect and extract identical adjacent repetitions of syllables in a string of

sounds; repeated exposure to syllable sequences containing immediate repetitions (ABB, mubaba) led to an increased response in left frontal regions as compared to syllable sequences containing random sequences (ABC, penaku) as measured by near infra red spectroscopy (near infrared spectroscopy (NIRS) is used to measure blood flow in the cortex from the scalp, (Gervain et al., 2008)).

By the age of three months, a baby can imitate the intonation of brief utterances and produce vowel-like sounds (Kuhl, 2004; Roug et al., 1989) but their vocal production is limited to non-speech vocalizations such as cries, screams, burps hiccups and laughter (Kuhl and Meltzoff, 1996; Nathani et al., 2006). The emergence of this behaviour parallels white matter development as observed in data obtained from diffusion tensor imaging, which shows that the arcuate fasciculus seems to develop relatively late: from around 1-4 months of age (Dubois et al., 2008). It is also broadly consistent with functional neuroimaging data that shows increased brain activity in the left superior temporal gyrus and Broca's area in three months olds listening to sentences as compared to an inter-trial rest period (Dehaene-Lambertz et al., 2006). Notably, by this time, the neural responses to the perception of speech in areas like the planum temporale (superior temporal gyrus) become more left lateralized (Dehaene-Lambertz et al., 2010). Work by Kuhl and Meltzoff (1996), showed that when 5 month old children listened to a vowel, they were consistently able to respond with a vowel sound that matched the sound they had heard (as opposed to producing a sound that did not match the sound they heard).

Five to eight months of age is a critical period of vocal development. At this time, infants show a significant decrease in non-speech vocalizations and an

increase in more speech like vocalizations such as babbling (Nathani et al., 2006). Initially, babbling is generally characterised by the repetition of strings of syllables such as 'bababa' or 'dadada' (Bergelson and Swingley, 2012). The rate at which infants produce syllables (about 3 per second), is thought to lay the foundation for speech production in later in life (Kent et al. 1991; see also Gervain and Mehler 2010). The rhythmic properties of babbling are thought to emerge earlier than any other property of language (Levitt and Aydelott Utman, 1992). At the same time, infants become more sensitive to perception of their native language (Cheour et al., 1998). For example, 6 month old infants are able to discriminate between native and foreign language vowel sounds (Kuhl et al., 1992). These changes correspond to a period of rapid myelination in frontal and temporal areas (Pujol et al., 2006). Neurally, 6-month old infants exhibit an increase in coupling between the superior temporal gyrus and Broca's area (Imada et al., 2006), suggesting that exposure to speech produces measurable changes in the connections between auditory and motor regions which are exploited to make the first speech-like vocalizations. At 9 months of age, the perception of familiar words evokes greater electrophysiological components that are larger in amplitude than unfamiliar words (Vihman et al., 2007), suggesting that the brain is much more efficient at processing novel stimuli. By about 10 months of age, the complexity of babbling increases substantially and is now characterised by alterations rather than repetitions of syllables (Oller et al., 2012) and the production of speech sounds (vowels) begins to resemble the child's native language (de Boysson-Bardies et al., 1989).

At around 12 months of age, a baby is able to produce their first word intelligible to adults (Oller et al., 2012). By about 18-24 months, a child's brain is 80%

of its adult mass and they begin to produce two-word utterances (Brown, 1973). They also have a vocabulary of about 300 words (Stoel-Gammon, 2011) a developmental staging point which coincides with the end of the period of rapid mylenation described by Pujol et al. (2006) who suggest that the ensuing vocabulary explosion might only be possible once sufficient myelination occurs. Although toddlers possess a relatively large vocabulary, they do not yet exhibit the typical compensatory responses in response to perturbations of auditory feedback of one's own voice seen in older children and adults (MacDonald et al., 2012). This is thought to suggest that the ability to correct speech develops only after children form stable internal representations of sounds.

By 4-5 years, the brain has reached approximately 90% of its adult mass (Dekaban and Sadowsky, 1978). Longitudinal studies show that the sensory and motor regions are the first to mature (i.e. exhibit a decrease in grey matter volume) in accordance with functional and developmental milestones (Gogtay et al. 2004; see also Toga et al. 2006). The density of white matter tracts like the arcuate fasciculus (connecting Broca's and Wernicke's areas) begins to increase linearly from around 5 years of age until about 16 years of age (Paus et al., 1999; Schmithorst et al., 2002). These age related increases in the arcuate fasciculus are almost exclusively driven by changes in the left hemisphere (Broce et al., 2015). Interestingly, whereas boys show a linear increase in the density of white matter with age, girls do not show evidence of a linear (or other) increase in white matter density with age (Blanton et al., 2004). These gender differences may have implications for explaining differing rates of speech impairments between the sexes, such as the higher rate of stuttering in boys compared to girls. A longitudinal study of brain development has shown

that this is also around the age of substantial increases in the thickness of grey matter in left Broca's area and bilateral temporal areas and that such thickening is positively correlated with vocabulary size (Sowell et al., 2004). Similar work by Lu et al. (2007) has shown that increases in white matter in left frontal regions is positively correlated with phonological processing scores, indicating that changes in white matter are functionally relevant for speech. However, not all tracts show age relate changes in the brain. For example, the microstructural properties of the frontal alsant tract do not show age related changes between the ages of 5 and 8 (Broce et al., 2015). Interestingly though, the same authors found the length of the tract is positively correlated with receptive language. Children at 4 years of age are able to produce words that differ from each other by only one consonant, suggesting that they already possess a relatively finely tuned speech production system (Goffman and Smith, 1999). Despite the structural changes described above, children's speech is still slower than adult's speech, a fact that is suggested to reflect a greater reliance on sensory feedback in children (Guenther and Hickok, 2015; Riely and Smith, 2003).

At six years of age, children's speech production systems are predominantly left lateralized (Wood et al., 2004), but there are still some differences in the time of peak activation of these areas, with a tendency for right temporal areas to be activated before left temporal areas and a greater lag in the activation of the left inferior frontal gyrus relative to the superior temporal cortex in children but not in adults (Brauer et al., 2008). Additionally, the connections between auditory and motor regions are still somewhat inefficient (Friederici et al., 2011). Indeed, Schlaggar et al. (2002) found substantial differences in the brain activity of children (aged 7-10) and adults (aged 21+) during the production of single words. The authors reached a

similar conclusion suggesting that because brain maturation was incomplete, children recruited slightly different regions to perform the same task. Between 7 and 10 years of age, the brain is still maturing. This is reflected somewhat in the differences between adults and children in terms of coordinating the articulatory musculature (Smith and Zelaznik, 2004).

The speech production abilities of children tend to resemble those of adults but the brain regions they engage are significantly more active (Gaillard et al., 2000), though this declines with age (Devous et al., 2006). By the time a child is 12 years old the child's brain has reached its full adult weight (Paus et al., 2001). Despite this, brain development is not yet complete and the brain is still undergoing significant changes. For example, several groups have reported that white matter volume continues to increase into at least the second decade of life (Pfefferbaum et al. 2000; Klingberg et al. 1999; see also Sowell et al. 2007; Toga et al. 2006; Sowell et al. 2002) and others have reported that in some areas of the brain (such as the temporal lobes), grey matter volume increases until at least 16 years of age (Giedd et al., 1999). Consistent with these findings, electrophysiological components change in amplitude and latency as children mature (Ponton et al., 2000). Interestingly, children who receive musical training show an enhanced P200 in response to tones relative to their non musical peers (Shahin et al., 2004). Throughout this time, a child's speech production abilities become increasingly refined, though the changes are much more subtle than at earlier ages. The studies above highlight that the ability to produce speech develops in conjunction with the maturation of auditory and motor regions. This likely occurs because speech places very high demands on systems governing auditory and motor activity.

2.3 The high demand on auditory and motor systems

The idea that speech production places significant demands on the auditory and motor systems is supported by data from experimental studies of adults and anecdotal observations. For example, even the simplest speech actions require complex coordination of lips, tongue, jaw, pharynx, larynx and respiratory system (for review, see Abbs et al., 1984). Electromyographic (EMG) recordings demonstrate that saying the word 'aba' recruits a wide variety of muscles that elevate or depress the upper and lower lips all within the span of 200-400ms (Abbs et al., 1984). Interesting insight into the demands that speech production places on the motor system can be gained by considering what happens to speech when such movements are constrained. A rather humorous argument for the demands speech places on the motor system comes from ventriloquism. Broadly defined, ventriloquism refers to the ability to make it seem like your voice is emanating from another location. Key to the successful performance of this act is to give the appearance of speaking without any discernible lip movement. However, even the most seasoned ventriloquist have difficulties with labial consonants (i.e. letters like f,v,p,b and m) which require both the upper and lower lips. For example, attempting the phrase, 'a bottle of beer' without moving one's lips is considerably difficult. Most amateur practitioners will greatly struggle with this phrase and have to substitute the labial 'b' with other letters. They would

likely end up saying something like ‘a gottle o gear’ or simply produce something completely unintelligible. This is of course an oversimplification of the articulatory muscles involved in speech as in reality much more than the lips are recruited to enable one to speak. Indeed, there is a striking resemblance between the brain areas engaged during speech production (Hirano et al., 1996) and controlled breathing (Ramsay et al., 1993) which highlights the fact that the motor activity associated with overt articulation involves more than just moving the mouth and tongue (Price, 2012).

The idea that speech production depends largely on the auditory system has been around for well over a century and is supported by evidence from a range of sources. The observation that there is a substantial decline in the quality of speech production following adult onset deafness (Waldstein, 1990) implies that auditory information is necessary to maintain clearly intelligible speech. The fact that there is also a decline in speech fluency in the presence of delayed auditory feedback (Black, 1951; Chesters et al., 2015; Lee, 1950) - in those who are otherwise proficient - implies that even small disruption to the timing of the auditory information can impair speech production. However, more convincing evidence for the involvement of the auditory system in speech production comes from the fact that lesions to the superior temporal gyrus, a region of the brain usually associated with auditory processing, leads to disruptions in the production rather than the perception of speech (Damasio and Damasio, 1980). Taken together, such evidence suggests that the auditory system plays an important role in the learning and maintenance of normal speech production.

2.4 A closer look at the neuroanatomy of speech production

The early studies of Broca, Wernicke and Licthceim, seem to imply that the speech production only requires auditory and motor areas. However, there is a major problem with forming an understanding of speech production based on lesion studies alone: It is logically impossible to rule out the involvement of other regions of the brain in speech production by investigating what happens to speech production when one area is damaged. In contrast to lesion studies, neuroimaging studies allow researchers to examine how a number of different brain areas contribute to speech production. Neuroimaging studies of young children have generally limited investigation to the functioning of auditory and motor areas. Such studies tend to examine speech perception rather than speech production (though see Sowman et al., 2014, for an exception). It is indeed possible that other areas are involved, but it may be difficult to detect them in children because of the limited types of studies that can be conducted. So, from such evidence it is difficult to appreciate the true complexity of speech production and it becomes problematic to determine how many different areas that might be involved in such a process.

Research in the 20th century would go on to show that many different cortical and subcortical regions of the brain are recruited for speech production (for review see Indefrey, 2011; Price, 2012). Notably, such studies have demonstrated that speech

production engages far more than just the auditory and motor cortices. The first systematic brain imaging study focusing on motor control of speech was conducted by Petersen et al. (1989). This group used PET to show that the cerebellum and the supplementary motor cortex were active under a variety of speech production conditions. These findings were later replicated using functional magnetic resonance imaging (fMRI). McCarthy et al. (1993) showed that the generation of words activated the left inferior frontal gyrus significantly more than did the repetition of words. Word repetition, semantically associating nouns and even translating between two languages, activates a broad network of frontal, temporal, cerebellar and putamenal areas (Klein et al., 1995). Similarly, the generation of verbs/nouns activates a network of regions including but not limited to the bilateral inferior frontal gyrus, superior temporal sulcus, caudate and thalamus (Warburton et al., 1996). Research on more naturalistic speech (Silbert et al., 2014) has documented similar findings. Naturalistic speech engages a unique subset of cortical and subcortical regions including the bilateral motor cortices, inferior frontal gyrus and caudate relative to listening to the same stimuli. It also activated a network of auditory regions that overlaps with regions activated in a comprehension condition, including the superior temporal gyrus, angular gyrus, temporal parietal junction, insula and medial prefrontal cortex (Silbert et al., 2014). Other groups have examined the complex interactions between resting state activity and speech. In addition to reporting the activation of a variety of cortical and subcortical regions, they show that the transition between resting state and speaking relies on the laryngeal motor cortex, the inferior parietal lobule and the cerebellum (Simonyan and Fuertinger, 2015). More recently, Flinker et al. (2015) recorded electrocortiographic activity in seven patients

undergoing brain surgery from areas including the motor cortex, superior temporal gyrus and the left inferior frontal gyrus. Such recordings allow for a careful examination of the brain dynamics of speech production because they have a high degree of temporal and spatial resolution. The authors measured brain activity in a variety of regions before and after overt articulation (which occurred at 1200ms post stimulus onset). While the motor cortex was active both before and during articulation, Broca's area exhibited a very different pattern of activation. Broca's area peaked in activity 340ms before overt articulation and did not appear to be active during articulation (i.e. after 1200ms). This finding confirmed the role of Broca's area in the planning of speech rather than the production of it.

The classical model of speech production developed by Broca, Wernicke and Licheim, was revolutionary in that it demonstrated particular areas of the brain were important for speech production and speech comprehension. At the same time however, these studies were also rudimentary and only provided a limited understanding of the brain areas involved in speech production. Due to the accumulation of neuroimaging evidence with an increasingly high degree of temporal and spatial resolution (see the above paragraph), the classical models are now obsolete (Poeppel and Hickok, 2004; Poeppel et al., 2012). Further, more recent work casts doubt over the role of areas once thought to be crucially involved in speech production. There is for example doubt over the whether damage to Broca's area causes Broca's aphasia. Even now, there is ongoing debate over the role of Broca's area in speech (Flinker et al., 2015), which despite many advancements, reinforces how far research has to go to fully understand this complex act.

Chapter 3

A Review of Normal Speech Production

3.1 Models of speech production

The following sections will, with reference to existing models of speech production, highlight the significant demands that speech production places on brain regions governing auditory and motor activity. They will demonstrate the need to predict both the current and future states of the articulators and the sensory feedback generated by speech production. Additionally, they will discuss the overlap in neural substrates engaged during the perception and production of rhythms and the auditory and motor regions recruited for speech production. Finally, they will discuss the predictive role of neural oscillations in speech production and their relation to auditory and motor activity and provide directions for future research.

3.2 The role of auditory feedback

Despite the complexity of speech production, speech is mostly error free. It has been suggested for example that people make approximately one to two errors for every thousand words spoken (Garnham et al., 1981). So how do people detect, correct and anticipate these errors? One means by which they are able to detect errors of speech is by recognising errors once they have made them. When a person speaks, they receive auditory (the sound of their voice) and somatosensory feedback (e.g. the position of their lips and tongue, the contact between their lips) feedback. Correcting errors by means of overt sensory feedback is an important part of one of the most detailed and influential models of speech production. According to the

directions into velocity of articulators (DIVA) model (Golfinopoulos et al., 2010; Guenther et al., 2006; Tourville and Guenther, 2011), people correct errors based on overt sensory feedback. The production of a syllable begins with the activation of the speech sound map (located in the left inferior frontal gyrus and the ventral premotor cortex). The term speech sound refers to the segment of speech that has its own motor program (such as a syllable) and, the term 'sound map' denotes that the goal of speech planning is to produce these 'speech sounds' rather than make the correct articulatory movements. Once the speech sound map is activated, motor commands are sent to the primary motor cortex via two systems: the feed forward system and the feedback system (which processes sensory (i.e. auditory) and somatosensory information). The speech sound map is connected to the auditory target map (the actual incoming signal which is a result of one's own speech). The auditory error map detects errors by comparing the inhibitory signals of the auditory target map (the signals expected as a result of one's own speech) and the auditory state map. If there is a mismatch between these two signals, then the auditory error map is activated and sends signals to the feedback control map (the right ventral premotor cortex and inferior frontal gyrus).

The correct mapping from auditory to motor commands is learnt through speech acquisition (Civier et al., 2010). During speech acquisition, somatosensory feedback is used to correct and improve the position of the articulators at every attempt to produce a syllable. Assuming the magnitude of the error is decreasing with each error, the feedforward command becomes more and more refined and there is less reliance on auditory feedback. In terms of the brain, the feedforward control system is hypothesized to involve a loop between the basal ganglia and the cortex

where speech is initiated in the supplementary motor area (SMA). (see Figure 3.1). Once these commands are learnt, somatosensory feedback is used to correct errors. When errors are made, corrective motor feedback is sent to the right ventral premotor cortex. Over a period of time these motor commands become refined to ultimately form feedforward commands.

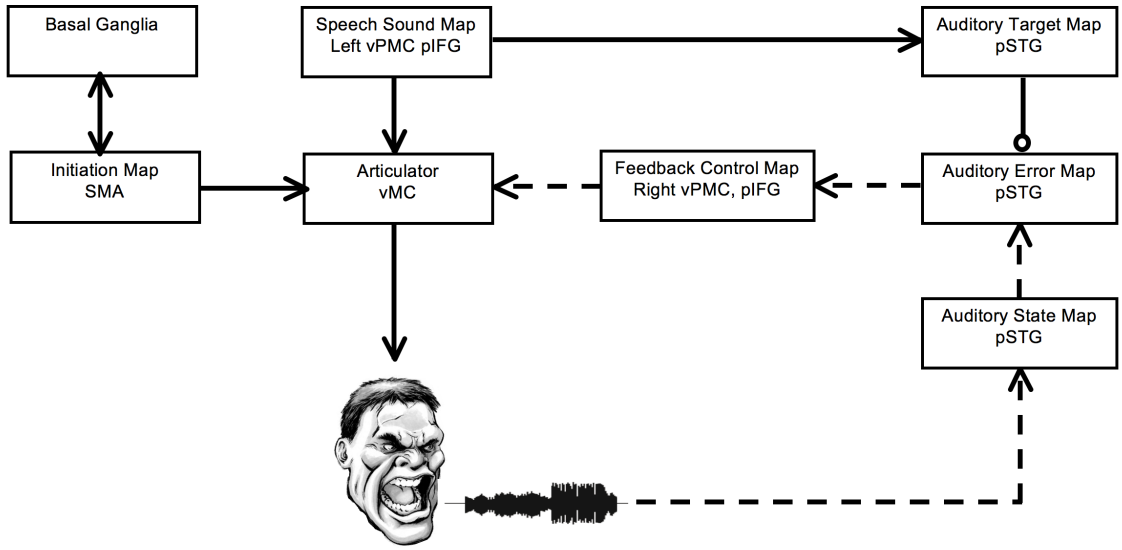

Figure 3.1: Simplified schematic of the Hierarchical State Feedback Control (HSFC) model of speech production. Each box represents a brain area. The solid lines denote feedforward signals and the dashed lines denote feedback signals. Importantly, the feedback signals can either be the result of internal (predicted) or external sensory feedback. The internal feedback allows errors to be corrected prior to articulation. Arrows represent excitatory signals and open circles represent inhibitory signals. The dotted line denotes the internal model. Note: the lower level somatosensory feedback loop (the second level of the hierarchy involving articulatory clusters) is not shown. Adapted from Guenther and Hickok (2015).

Notably, the SMA has a central role in the initiation of speech (Bohland and Guenther, 2006). The basal ganglia are thought to determine when to launch feedforward commands for the next sound to be produced. A more recent instantiation of the DIVA model, termed the gradient ordered directions into velocity of articulators (GODIVA, Bohland et al. 2010), describes how the basal ganglia (thought to receive copies of motor commands or efference copies from the motor cortex) plays

a role in the production of multisyllabic utterances. For example, the basal ganglia are thought to trigger the transition from one syllable to the next, based on copies of motor commands they receive from the motor cortex (Civier et al., 2013). The main problem with auditory feedback is that it cannot handle large errors in speech. Under most circumstances, when errors are relatively small, auditory feedback is sufficient for correction.

Sometimes individuals appear to correct errors in speech very rapidly such as the statement 'No one is the s-repository of all wisdom'. This is fundamentally different than the example above because the error is detected immediately after the first phoneme of the word. In such cases, the speaker does not necessarily have the time to monitor the overt auditory and somatosensory feedback (Nozari et al., 2011). Despite appearances, this form of error correction is actually relatively slow. Indeed correction can occur within 65ms before the error is noticed (Civier et al., 2010). Despite being quite rapid, feedback is subject to inevitable delays. By the time the person has made lip movements and articulated a given sound, the feedback received no longer matches the actual position of the lips and will therefore be wrong (Hickok, 2012). When the brain realises that the tongue and lips are in the wrong position it will send a corrective signal based on somatosensory and auditory feedback. This correction signal corresponds to the current (incorrect) position of the articulators. Because the articulators are moving, this signal will arrive at a time in the future when the articulators are already in a different position. Put simply, the 'corrective' feedback will be wrong. It should therefore be obvious that while auditory feedback is important for fluent speech production, in isolation, it is inefficient. This implies that there must be another means by which errors of speech are corrected.

3.3 The need to predict sensory feedback

So how can the problem be solved? One particularly elegant solution is to incorporate what is known as a forward model. The concept of a 'forward model' has strongly influenced the general discourse of speech motor control and is an important feature in many recent models of speech production (e.g. hierarchical state feedback control (HSFC) model). It enables prediction of the sensory and somatosensory consequences of our own actions before sensory feedback is received. The ability to make accurate predictions about the features (content), location (space) and moment (timing) of motor movements relies on an internal model and appears as a common theme in motor control literature. Internal models are useful because, as illustrated above, they enable us to correct errors before they occur. The brain was originally viewed as a tool that simply reacted to external stimuli but it is now being realised that the brain can react to what it expects will happen (Engel et al., 2001). That is to say, the brain is anticipating the content of upcoming stimuli and is predictive rather than purely reactive (ten Oever et al., 2014). The notion that the brain is essentially able to anticipate errors suggests it is responding to something other than stimulus driven feedback marked a significant departure in how researchers viewed it's computational power. Notably, while the DIVA and GODIVA models are particularly detailed accounts of speech production, they do not incorporate an internal feedback mechanism (Hickok, 2012).

Models that do incorporate such an internal feedback mechanism of compar-

ing the predicted (and actual) feedback from sensory and somatosensory systems are known as state feedback control (SFC) models. In this formulation of speech production, articulation begins with the activation of both auditory and motor systems to initiate jaw movements that correspond to the production of individual phonemes (Guenther and Hickok, 2015; Hickok, 2012). The SFC model consists of several major components: a controller, an effector, an internal model and a conceptual system. Many of these components can be localized in the human brain and each has a specific role in speech production. The goal of speech production in the SFC model is to hit 'auditory targets'. This process begins with retrieval of a word from a lexicon which codes the grammatical, but not phonological, form of the word and activates the auditory system. The controller sends motor commands to the effector, which in the case of speech production, is the vocal tract. The controller also sends a copy of this motor command to the internal model. The internal model is split into three main parts: a motor phonological system, an auditory phonological system and a translational system. The motor phonological system makes predictions about the current and future position of the articulators) and is localized to the premotor cortex. The auditory phonological system makes predictions about the sensory consequences of actions and is localized to the superior temporal gyrus. These two systems are linked via a translational system found in the Sylvian fissure at the boundary of the temporal and parietal cortices of the brain (often referred to as area SpT, Hickok et al., 2011; Hickok, 2012). Deviations between the predicted and actual sensory feedback generate an error signal that is used to correct the movement of the vocal tract. Error signals can be generated either because the desired motor command was not executed properly or sensory feedback has been altered.

In recent years, this integrated SFC model has been expanded. The HSFC model (Hickok, 2012), differs from the SFC model in two main respects. First the HSFC model splits the motor internal models of the phonological system and the auditory phonological system across two levels, each with their own input and output. The higher level processes auditory information and 'maps' syllables whereas the lower level processes somatosensory information and 'maps' phonemes. Notably, the motor phonological system that codes syllables is localized to the left inferior frontal gyrus and outputs to area SpT while the lower level outputs to the premotor/primary motor cortex. (see Figure 3.2).

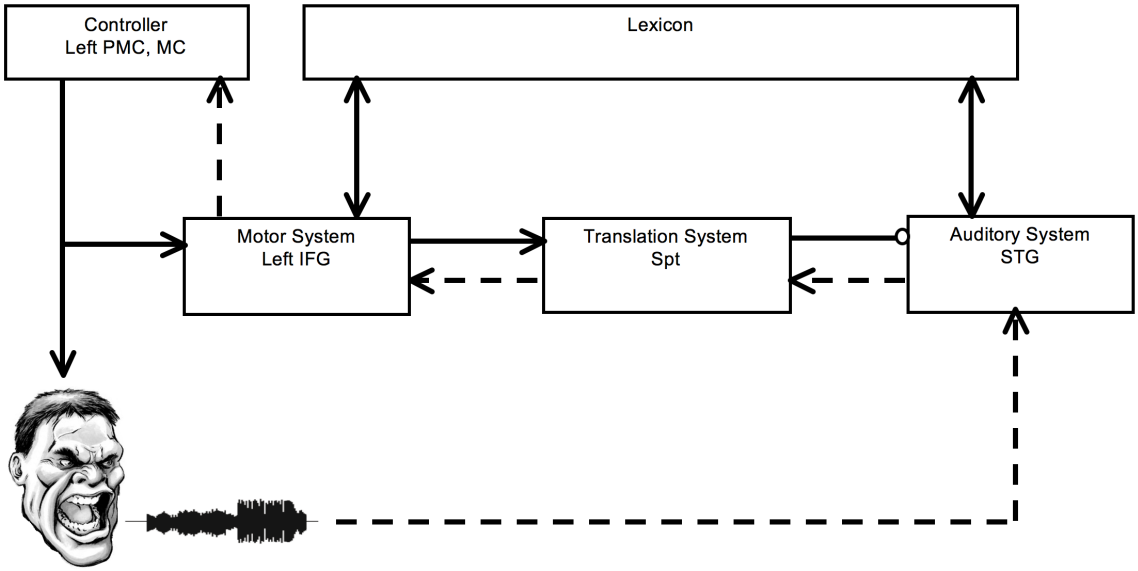

Figure 3.2: Simplified schematic of the Hierarchical State Feedback Control (HSFC) model of speech production. Each box represents a brain area. The solid lines denote feedforward signals and the dashed lines denote feedback signals. Importantly, the feedback signals can either be the result of internal (predicted) or external sensory feedback. The internal feedback allows errors to be corrected prior to articulation. Arrows represent excitatory signals and open circles represent inhibitory signals. The dotted line denotes the internal model. Note: the lower level somatosensory feedback loop (the second level of the hierarchy involving articulatory clusters) is not shown. Adapted from Guenther and Hickok (2015).

An efference copy is not a true part of the HSFC model as it is implicitly built into the motor planning process. Error correction is predominantly achieved

via the auditory phonological system. The system is always ready to send an error signal to the motor system unless it receives an inhibitory signal from the motor phonological system via area SpT. Notably, this inhibitory signal is the HSFC model's equivalent of a copy of a motor command. When the motor and auditory units - programs corresponding to form the intended word - 'match', the signals cancel each other out and speech continues as per normal. If however there is a mismatch, the motor units inhibit the auditory units until the correct ones are selected. Once the correct auditory units are selected, speech production can proceed as per normal. While this is a fairly compelling account of feedforward and feedback mechanisms in the domain of speech, the model is incomplete. Hickok and Poeppel (2007) note that the integrated SFC model neglects subcortical brain regions such as the basal ganglia which are known to be involved in motor control (Alexander et al., 1986; Alexander and Crutcher, 1990). This shortcoming becomes particularly glaring when one considers the fact that the basal ganglia plays an important role in the integration of auditory and motor information (Hove et al., 2013). Further, as noted above, this structure also plays an important role in the extended GODIVA model of speech production (Civier et al., 2013).

There are a number of important similarities and differences between the DIVA/GODIVA and the HSFC models. Firstly, the HSFC is a box and arrow model that describes how brain regions perform various functions. In contrast to this, the DIVA/GODIVA is a computational model. Computational models can be used to quantitatively test predictions about acoustics, kinematics and brain activation. The GODIVA model can, for example, be used to test the effects of reductions in white matter or how manipulations of levels of dopamine impact speech production (Civier

et al., 2013). Both models incorporate separate feedback loops. Secondly, whereas the DIVA/GODIVA model only makes use of external sensory feedback to correct errors, the HSFC model theorizes the existence of both internal and external sensory feedback. The DIVA/GODIVA model incorporates subcortical structures such as the basal ganglia but the HSFC does not. In spite of such differences, there are also significant similarities. In both models speech planning is roughly at the syllable level. Both the HSFC/GODIVA model include a means to translate auditory to motor information (and vice versa). In the HSFC model this is achieved in area SpT whereas in the GODIVA model this is achieved in the projections from the auditory error map (located in PT and pSTG) and the feedback control map (located in the right ventral PMC). More generally, both models also rely on some form of prediction. In the case of the HSFC model this is dependent on both the premotor cortex and left inferior frontal gyrus and the superior temporal gyrus whereas in the DIVA/GODIVA model, this is dependent on the premotor cortex and the putamen. Finally, in both models errors arise when there are differences between the actual and predicted position of the articulators and between the actual and predicted sensory feedback. Therefore, if one accepts these models, the brain must accurately predict auditory and somatosensory feedback (Max et al., 2004). If the brain is unable to accurately predict auditory and somatosensory feedback, speech fluency may be disturbed (Max et al., 2004). Two obvious questions come to mind: can this prediction be localized to specific areas of the brain and how might it be computed?

3.4 The importance of rhythm for speech production

In the preceding discussion, I have suggested that speech requires some form of prediction. This has largely been confined to predicting the auditory or somatosensory consequences of actions. Clear evidence exists in the realm of speech perception that individuals predict 'what' will happen and that such prediction is used to facilitate speech processing. For example, upon hearing the phrase 'the child eats the-', a child will tend to fixate on the edible objects within a visual scene prior to hearing the word 'cake' rather than inedible objects like tennis balls or concrete slabs. The pattern of eye movements appears to indicate that children are predicting 'what' will occur next (Mani and Huettig, 2012). Interestingly, children with a larger vocabulary formed stronger predictions and the authors found that a larger vocabulary size was correlated with improved speech production skills. Similarly, DeLong et al. (2005) showed that adults exhibit different neural responses depending on whether they are presented with the word 'an' or 'a'. This was thought to indicate that adults use words in a sentence to predict the likelihood of upcoming words. Dell and Chang (2014) asserted that if such knowledge can be used in the context of speech perception, then it could also be sued to facilitate speech production.

Research using the mismatch negativity (MMN) paradigm also gives weight to the contention that children are predicting 'what' they will hear next. The MMN paradigm typically presents subjects with a train of standard sounds (e.g. pa pa pa pa pa) and occasionally presents a deviant (e.g. pa pa da pa pa). The difference in the neural response to what is heard (the deviant da) and what is expected (the standard

pa) results in a component that peaks around 150-250ms after stimulus onset, known as the mismatch negativity response (for review see Näätänen, 2001; Näätänen et al., 2007), and is thought by some to index predictability. Interestingly, recent research shows that predicting 'what' can be influenced by temporal regularity. Kotz et al. (2014) compared the electroencephalographic response to deviant tones embedded in either rhythmic or arrhythmic trains of standard sounds. The authors found that the amplitude of responses to the deviant sounds was significantly greater in the rhythmic condition as compared to the arrhythmic condition. A rhythmic context elicited a greater sensitivity to violations of predictability. Being able to predict 'what' is clearly important for speech production, however the experiment by Kotz et al. (2014) demonstrates that such ability is greatly influenced by the ability to predict 'when'. Likewise, Costa-Faidella et al. (2011) showed that presenting pure tones of varying frequencies in an isochronous condition enhances the early repetition positivity - an auditory evoked potential indexing sensory memory - as compared to presenting tones at a non isochronous interval. Although such findings have not yet been demonstrated in the context of speech production (as far as I am aware of), rhythm or prediction is known to have a beneficial effect on speech production. Indeed, as mentioned previously, speaking in time with metronomes can enhance the fluency of adults who stutter (e.g. Toyomura et al., 2011, 2015). The importance of being able to predict 'when' in speech is also highlighted by examining the effects of delayed auditory feedback. Delayed auditory feedback generally creates profound dysfluencies in individuals who are normally fluent. This is particularly interesting because speaking under delayed auditory feedback presumably involves a correct prediction about what sensory feedback is going to be received, but an incorrect

prediction about when that feedback will be received (Black, 1951; Chesters et al., 2015; Lee, 1950). In particular, impairments in the timing of this sensory feedback have been associated with speech disorders such as stuttering (e.g. Cai et al., 2014a). Therefore, not only is predicting 'what' important for fluent speech production, but so too is the ability to predict 'when'.

Given the importance of timing in motor production, investigating speech production in the time domain is warranted. It should not be surprising then that for speech to be fluent, it must have some sort of recognisable temporal structure. This indeed appears to be the case since speech events can decomposed into discrete events (such as phonemes, syllables, words and phrases see Kotz and Schwartze 2010), each of which occurs at very short timescales. The ability to predict when things will happen relies in large part on having established temporal regularities (Arnal, 2012). Perhaps the most logical place to start examining temporal prediction is to begin by examining rhythm (Grahn, 2012) as a sense of rhythm is essential for the representation of time (Guaïtella, 1999) and vice versa. The idea that rhythm is a fundamental part of normal speech production has a long history and its roots can be traced back to the writings of Thomson (1923) and Sonnenschein (1923) (for review see Kohler, 2009). These authors argued that the concept of 'rhythm' in speech was a very different phenomenon to the concept of 'rhythm' in music. Other scholars disagreed, highlighting the fact that people describe numerous musical and non musical events as being 'rhythmical' which suggests that the notion of rhythm should be applied more generally (see Knowles, 1974). These debates most likely stem from the fact that speech is not perfectly rhythmic but rather is quasi-rhythmic, containing words that occur at slightly irregular yet temporally predictable

intervals (Peelle and Davis, 2012). The definition of rhythm I adopt here is the same and I stress that an element of predictability is inherent in the concept of rhythm. A number of experimental studies naturally arose from the controversy over the theoretical concept of rhythm.

The logic behind such studies was fairly intuitive. Typically they involved recording English speakers reading text and marking the durations between stressed syllables. Stressed syllables were thought to occur at predictable times (Abercrombie et al., 1967; Pike, 1945). A number of subsequent studies failed to yield convincing evidence of rhythmicity in speech. Whereas some researchers found support for the involvement of rhythm in speech (e.g. Lashley, 1951), others did not (e.g. Classe, 1939). This trend continued and the literature was plagued by inconclusive results (for review see Martin, 1972). Several dichotic listening tasks purportedly showed that while speech was processed by the left hemisphere, non-speech was processed by the right hemisphere. This was challenged by Robinson and Solomon (1974), who found that both speech and rhythm were localized to the left hemisphere. The lack of agreement among published studies highlighted that the perceived importance of rhythm for speech may be unjustified. Notably, this idea still persists in the literature today (e.g. Nolan and Jeon, 2014). As a result of this work, research into the involvement of rhythm and temporal information in speech was given substantially less attention than it had previously received. Perhaps a more nuanced approach than studying spectral properties of speech is required to tackle the question of whether or not speech is rhythmic.

If speech is fundamentally rhythmic then there should be experimental evi-

dence showing that there is a relationship between rhythmic behaviours and speech. A growing body of evidence suggests speech perception is rhythmic (see for review, Peelle and Davis, 2012; Arnal and Giraud, 2012; Ghazanfar and Takahashi, 2014; Giraud and Poeppel, 2012a). In particular, the perception of speech (prosody) is correlated with the perception of rhythm (Hausen et al., 2013). However, just because speech can be perceived as rhythmic, does not necessitate that speech production is actually rhythmic. Multisyllabic babbling is frequently perceived as rhythmic and emerges at the same time as other rhythmic body movements (for review see Kent et al. 1991 see also Ejiri 1998). Importantly, rhythmic babbling is thought to form the building blocks of speech production (Gervain and Mehler, 2010; Kent et al., 1991). While some authors claim that there is a discontinuity between babbling and speech production (Fry, 1966; Jakobson, 1941), there is evidence to suggest that babbling still persists even after children produce their first words (Elbers, 1982) and further that there is a high similarity between the phonetic characteristics of first words and babbling (Stoel-Gammon and Cooper, 1984). As such, babbling - and its rhythmic aspects - can be regarded as a true stage of speech development rather than a precursor to it. Stronger evidence for the involvement of rhythm in speech production comes from the fact that neonates (1-14 days old) synchronise their movement to the speech of adult speakers (Condon and Sander, 1974). Likewise, adults are able to synchronise their speech to one another (Himberg et al., 2015; Cummins, 2003). This highlights that while speech may not be perfectly rhythmic it is at least predictable enough to enable the coordination of speech production. Had speech been produced at random or unpredictable temporal intervals, subjects would have found it very difficult if not impossible to perform this task. Thus, it can be argued that speech

like other biological signals exhibits strong regularities (Arnal, 2012).

Along a similar line of reasoning, it has been claimed that the tendency to synchronise movements with auditory beats occurs only in those species capable of vocal learning (specifically birds, cetaceans, and pinnipeds but not non-human primates) (Patel et al., 2009). This phenomenon is thought to be dependent on a privileged connection between auditory and motor regions (Friston et al., 2015; Morillon and Schroeder, 2015), something that, as mentioned above, is also important for speech production. Interestingly, some studies have reported activation in the left inferior frontal gyrus during the perception of an isochronous rhythm (e.g. Grahn et al., 2007; Grahn and Rowe, 2009) and others when tapping to a rhythmic beat (Mayville et al., 2002; Schaal et al., 2004; Witt and Stevens, 2013). Because the left inferior frontal gyrus is classically associated with speech production, such results suggest that the perception of rhythm could influence the production of speech. This idea fits comfortably with the observation that being exposed to an external rhythm can enhance speech production in pre-lingually deaf children (Cason et al., 2015), people who stutter (Toyomura et al., 2011, 2015) and in Parkinson's Disease (Thaut et al., 2001). Taken together, these studies show that the perception of rhythm and the production of non-speech movements both recruit the left inferior frontal gyrus, an area widely known to be involved in speech production.

More generally, the contention that speech production is fundamentally rhythmic (Kotz and Schwartze, 2010) implies that models of speech production should contain brain areas that are specifically dedicated to, or can intrinsically process time. How the brain processes time is largely dependent on the manner in which

time is measured. Time can either be measured relative to a beat or, when no such beat is available, be encoded more discretely like a stopwatch where 'time' is encoded as a continuously increasing variable (Merchant et al., 2015). By describing speech as 'rhythmic' or 'quasi-rhythmic' it could be thought that speech tends to recruit areas (such as the basal ganglia) that mediate beat-based timing rather than those (such as the cerebellum) that mediate absolute timing. While this is a reasonable conclusion, the distinction between the different forms of timing and their neural substrates is not entirely unclear. For instance, there are anatomical connections between the basal ganglia and cerebellum and one system may reinforce or optimize the other (Teki et al. 2011a, see also Teki et al. 2011b). As such, it is reasonable to expect that speech may involve both systems, albeit to various degrees. The mechanisms used to process time, whether relative or beat-based, also depends on the modality (see for review Merchant et al., 2013). Because a person does not generally receive visual feedback of motor movement during their own speech, I omit reference to the contribution of visual areas to timing and rhythm and instead tend to focus on brain regions that underlie responses to auditory rhythms. In contrast to this, the importance of auditory feedback is underscored by the effect of adult onset deafness on speech: the lack of auditory feedback eventually results in a decline in the quality of speech production (Waldstein, 1990).

The idea that brain regions are specialised for particular functions has guided much research in the 21st century. However, it is also well established that a single brain region can participate in multiple and sometimes distinct processes. For example, Buckner et al. (2008) has demonstrated the existence of a so-called default network - a series of brain regions activated by a variety of different and seemingly

unrelated cognitive tasks. From this perspective, it could be argued that neural overlap does not necessarily equate to shared function (see for review Peretz et al., 2015). This is a valid concern that deserves to be addressed. It is important to acknowledge the fact that there are considerable differences in the pitch and rhythm of speech and music (Peretz et al., 2015). One explanation for seemingly overlapping responses to speech and music/rhythm is that there are functionally distinct populations of cells within the same area responding to the same cognitive processes. Notably, although some authors have used multi-voxel pattern analysis to show specific voxels are tuned to the either pitch of music and speech (e.g. Merrill et al., 2012), I am aware of no studies using this technique to examine differences in rhythm of speech and music. Yet, even if such a difference were found, it would not change the fact that different voxels are still tuned to rhythm of either speech or music. A second possibility is that the overlapping activation reflects a common process within the same cells. While an interesting concept, further discussion of this issue is outside the scope of this dissertation.

There is evidence from invasive and non-invasive studies that brain regions supporting motor control (i.e. articulation) and sensory processing (i.e. audition) - components of the HSFC model and the GODIVA model - are also involved in temporal processing. For example, the SMA is frequently activated in neuroimaging studies of speech, so much so, that it was given equal importance with Broca's area in terms of its contribution to speech production (MacNeilage, 1998). Different portions of the SMA are specifically engaged in the selection, encoding/sequencing and articulation of words (Alario et al., 2006) while electrical stimulation of the SMA leads subjects to produce involuntary repetitive sounds like 'dadadada' or 'tetetetete'.

(e.g. Penfield and Jasper, 1954; Penfield and Welch, 1951). These patterns of speech strongly resemble the rhythmic babbling of infants and suggest that rhythmic motor programs are an essential component of speech (Thelen, 1981). Lesions to the SMA often result in impairments to speech production (e.g. Ziegler et al., 1997) and also interfere with the ability to reproduce rhythmic movements (Halsband et al., 1993). Although not specifically focusing on speech research, a recent meta analysis found that the SMA (along with the right inferior frontal gyrus) formed part of a 'core timing network' as they were the only two regions consistently activated across a variety of different timing tasks (Wiener et al., 2010). Interestingly, subjects who perceive time as lasting longer, display greater activation in both of these areas (Tipples et al., 2013). In a later meta analysis, Schwartze et al. (2012) found that different portions of the SMA and preSMA were responsible for different aspects of temporal control. Whereas the preSMA was involved in sensory (i.e. little or no movement), non sequential (less than 3 successive events used to establish temporal structure), and suprasecond (intervals greater than 1000 ms) temporal processing, the SMA-proper was involved in the sensorimotor (requiring some form of movement other than a button press), sequential (temporal structure established in 3 or more successive intervals) and subsecond timing (intervals less than 1000 ms). Thus there is some evidence that motor regions of the brain are able to process time. However, it is important to note that these are not the only areas capable of doing so.

Auditory areas are also able to process time and speech. Binder et al. (1996) used fMRI to show the left planum temporale displayed similarly increased activation in response to listening to speech and tones while Bengtsson et al. (2005) demonstrated that the same area was also enlisted during the production of rhyth-

mic finger sequences. Auditory areas are engaged in response to both self-generated speech and recordings of one's own voice (e.g. Zheng et al., 2010). Accordingly, during speech production, the amplitude of the N100m (the neuromagnetic equivalent of the N100) response to self-generated speech is attenuated relative to playback and to pitch-shifted auditory feedback (Heinks-Maldonado et al., 2006; Beal et al., 2011). Interestingly, the N100m has also been linked to temporal processing. Tecchio et al. (2000) has demonstrated that the amplitude of the N100m can be influenced by varying interestimulus intervals as a percentage of a standard interval. Notably, this occurs not only for perceptible intervals (differences of 20%) but also for imperceptible intervals (differences of 2%). The amplitude of the N100m elicited by rhythmic sounds is much smaller in silence and larger in noise than responses elicited by arrhythmic sounds (Okamoto et al., 2013). Thus the auditory cortex is able to use temporal regularity to modulate neural responses. Research using the MMN paradigm provides evidence that the auditory cortex is sensitive to deviations in stimulus onset intervals. Lai et al. (2011) showed that shortening or lengthening the IOI by 10% elicited an MMN response to tones. Similarly, Kisley et al. (2004) demonstrated that the MMN response could be elicited by changes as small as 3.75% of the IOI and that magnitude of this response was dependent on the deviation from the IOI. Furthermore, the tempo of an auditory stimulus can influence the ability to make wrist flexions to an isochronous beat (Bravi et al., 2014). Moreover, auditory areas can track the rate of stimulation, as evidenced by peaks of neuromagnetic activity around the onset of the stimulus (Cirelli et al., 2014; Fujioka et al., 2012), detect omissions of stimuli in regular trains of sound (e.g. Fujioka et al., 2009; Snyder and Large, 2005; Zanto et al., 2006) and are sensitive to violations in the duration

of tones (e.g. Molholm et al., 2005).

In addition to the aforementioned cortical areas, a number of subcortical regions like the basal ganglia and the cerebellum are frequently implicated in various aspects of speech production (Civier et al. 2013; Fujii and Wan 2014; Ackermann 2008 and see also Jin and Costa 2015) and are the topic of much debate in the realm of temporal processing (e.g. Ivry and Schlerf, 2008; Ivry and Keele, 1989; Ivry and Spencer, 2004; Kotz and Schwartze, 2011; Matell and Meck, 2004; Etchell et al., 2014a; Steen et al., 2015). The basal ganglia are linked to auditory and motor areas (Alexander et al., 1989), involved in different speech rates (Ackermann and Riecker, 2010; Riecker et al., 2002), are thought to receive copies of motor commands (Civier et al., 2013) and have been observed to be activated before voice onset (Watson and Montgomery, 2006). Riecker et al. (2002) found that the basal ganglia were not active during isochronous rhythmic production of the syllable 'pa', but were active in a non-isochronous rhythmic condition. Such a finding may however be attributable to the baseline condition in which subjects listened to isochronous vocalizations of the syllable pa (see below) and so the lack of activation may not be representative of the basal ganglia in speech. The putamen is known to activate in response to isochronous stimulation (Grahn et al., 2007; Grahn and Rowe, 2009), but appears to be particularly active in response to beat intervals of 500-700ms (Riecker et al., 2003, 2006). Additionally, while there is some level of activity in response to the detection of regularity, the putamen is more responsive to rhythms that have already been internalized (Merchant et al., 2015). Work by Rao et al. (1997) indicates that the basal ganglia are active during continuation tapping (tapping once a metronome has been removed) as compared to rest, but not during synchronisation tapping (tapping

in time with a metronome) as compared to rest (Rao et al., 1997). The basal ganglia also help to facilitate sensorimotor synchronisation independent of modality (Hove et al., 2013). Interestingly, individuals with bilateral lesions to the basal ganglia perform particularly poorly on the continuation phase of a tapping task (Coslett et al., 2010), a result which agrees with its proposed role in internalization (Coull et al., 2013; Etchell et al., 2014a). Further evidence for the involvement of the basal ganglia in temporal processing and speech comes from studies investigating the effects of dopamine. Pharmacological manipulation of dopamine can influence the perception of temporal intervals (Coull et al., 2012; Wiener et al., 2011) as well as speech production (for review see Rosenberger, 1980). Notably, a recent study found the use of dopamine to treat Parkinson's Disease caused profound stuttering like dysfluencies in some subjects (Tykalová et al., 2015).

In a similar vein, the cerebellum is thought to be responsible for controlling acceleration of orofacial gestures, timing of complex articulatory gestures and controlling brainstem reflexes that monitor respiratory and laryngeal activity (for review see Ackermann and Hertrich, 2000). As noted above, the cerebellum forms an important component of the HSFC model (Hickok, 2012), is active during speech and singing (Riecker et al., 2000) and exhibits greater activation for paced finger tapping as compared to listening to isochronous sounds (Thaut et al., 2008) or to rest (Rao et al., 1997). Additionally, it has been shown that both lesions (Schlerf et al., 2007) and transcranial magnetic simulation (TMS) of the cerebellum (Del Olmo et al., 2007; Théoret et al., 2001) impair variability of paced finger tapping. This is somewhat paradoxical given that the cerebellum is thought to be more involved in absolute rather than beat-based timing. However, before the beat has been internal-

ized (i.e. the synchronisation phase), one would tend to rely more on absolute than beat-based timing. Conversely, once the beat has been internalized (the continuation phase) one would become more reliant on beat-based timing despite the fact that there is no beat. Interestingly, damage to the cerebellum can result in a form of dysarthria characterised by a reduction in the variation of syllable duration referred to as isochronous syllable pacing (Ackermann et al., 2007). The fact that speech appears relatively isochronous perhaps suggests there is greater reliance on the basal ganglia, which as shown above, are responsible for the perception and production of rhythmic movements and sounds. These studies show there is a considerable degree of overlap of the brain regions involved in speech production and the processing of rhythmic auditory stimuli and movements.

3.5 The importance of brain rhythms for speech production

The studies above indicate that speech production involves a complex network of brain regions. It is important to point out that they do not operate in isolation. How might these areas communicate? One means by which this could be achieved is via neural oscillations (see review by Fries, 2005). Neural oscillations are ubiquitous in the human brain and can be recorded invasively or non-invasively using tools like MEG and EEG. The term is generally used to describe rhythmic fluctuations in local field potentials, caused by the synchronisation of transmembrane currents in

populations of neurons (Thut et al., 2012). Put simply, neural oscillations represent cyclic changes in the excitation and inhibition of populations of neurons. They are generally described according to the speed of their cycle (e.g. 5-8 Hz is the delta band, 8-12 Hz is the alpha band, 12-30 Hz is the beta band, 30-100 Hz is the gamma band). However, the identification of neural oscillations based on a canonical predefined frequency range is somewhat restrictive because there are times when one frequency range overlaps another (e.g. Zanto et al., 2006). While these are useful descriptors, it is perhaps also sensible to allow for some degree of flexibility and identify oscillations based on the cognitive function(s) that they are associated with (Bressler and Richter, 2015). That being said, neural oscillations have functional significance over and above fostering communication between different areas of the brain. Oscillations may underpin the neurophysiological substrate for prediction in the time domain (Morillon and Schroeder, 2015). The view that neural oscillations are also useful for processing time (i.e. rhythm) has received extensive support (Arnal, 2012; Buhusi and Meck, 2005; Engel et al., 2001; Matell and Meck, 2004; Thut et al., 2012; Womelsdorf and Fries, 2007).

In agreement with these ideas, certain low frequencies (delta, alpha and beta) are particularly well suited to tracking timescales that correspond to the frequencies of human behaviours and enabling the perception of and entrainment to rhythms (for review see Arnal, 2012; Merchant et al., 2015). For example, the gamma band has been related to anticipation and the perception of a rhythmic meter whilst also having some relation to attention (Zanto et al., 2006). Alternatively, alpha band activity is desynchronised at the expected onset of a predictable stimulus (Rohenkohl and Nobre, 2011; Thut et al., 2006). Furthermore, oscillations in the delta range align

with predictable rhythmic stimuli such as tones (Nozaradan et al., 2011, 2012) and speech (Giraud et al., 2007). Interestingly, presenting isochronous auditory stimuli at frequencies within the delta range modulates the slope of beta band rebound such that it peaks around the time of the next expected stimulus onset (Cirelli et al., 2014; Fujioka et al., 2012). In the very same way that brain regions to not operate in isolation, frequency bands also do not operate in isolation. Saleh et al. (2010) asserted that the beta amplitude and the delta phase work in concert to facilitate response to predictable and task relevant cues. Likewise, it is thought that the phase and amplitude of different frequencies interact with one another. Lakatos et al. (2005) showed using intracranial recordings in macaques that delta phase entrains the amplitude of theta response and that the theta phase entrains the gamma amplitude to optimize processing of rhythmic sounds. The fact that neural oscillations are crucial for predicting rhythmic stimuli, taken together with the fact that speech production engages many of the brain areas recruited during the processing of rhythm, suggests that neural oscillations may be crucial for fluent speech production. Moreover, there is already some evidence for the involvement of oscillations in speech production. For example, Morillon et al. (2010) point out that syllables and phonemes correspond to the movement of the jaw and tongue which are associated with fluctuations in power in the 4Hz range (delta) and 35-40Hz (gamma) range.

Since speech production unfolds over time and requires the interaction of the auditory and motor systems, extracting temporal regularities associated with speech might be expected to involve a frequency sensitive to both auditory and motor information. One such frequency is the beta band, which generally refers to

oscillations between (12-30 Hz). This frequency range is typically associated with the preparation and execution of movement (for review see Kilavik et al., 2013; Pavlidou et al., 2014). Beta power decreases prior to (Pfurtscheller et al., 1998), and when imagining (Schnitzler et al., 1997) or observing, movement (Babiloni et al., 2002; Muthukumaraswamy and Johnson, 2004). For this reason, some authors have linked the beta band with maintaining the status quo (Engel and Fries, 2010) or suggested that it is related to the likelihood that a new action will need to be performed (Jenkinson and Brown, 2011). In addition to being related to motor activity, the beta band is sensitive to incoming auditory stimuli. For example, the oscillatory response to imagining a tone on the beat is significantly larger than when imagining a tone occurring off the beat (Iversen et al., 2009). Passively listening to isochronous sounds modulates beta band activity in auditory and motor regions of the brain (Cirelli et al., 2014; Fujioka et al., 2009, 2012, see chapters 10-11). Notably, this is perhaps similar to how the perception of speech activates motor regions of the brain (Silbert et al., 2014; Wilson et al., 2004). Recently Arnal et al. (2014) showed there was an increase in cortical beta power prior to correctly judging whether or not a target tone had been delayed in time. Interestingly, these beta oscillations were coupled with delta oscillations and entrained to the beat during correct temporal judgements. It has also been shown that the expectation of a stimulus modulates beta band activity in the absence of attention (Todorovic et al., 2015). These are exactly the sorts of responses one would expect if the beta band were involved in processing auditory, motor and temporal information. Given the importance of auditory and motor information for speech production, the beta band may be important for speech production.

The beta band may not be epiphenomenal to speech production, but rather crucial for it to occur. Several theoretical and empirical studies already link the beta band to prediction in the form of top down control (Arnal and Giraud, 2012; Arnal, 2012; Buschman and Miller, 2007; Jenson et al., 2014a; Engel and Fries, 2010; Friston et al., 2015; Kilavik et al., 2013; Siegel et al., 2012; Wang, 2010). It has also been hypothesized that this prediction relies on the degree of phase synchronisation between different frequency bands (Bressler and Richter, 2015). It has been suggested that predicting 'what' and 'when' are distinct processes (Buzsáki and Draguhn, 2004), but this is not necessarily the case. Indeed, modulation of the beta band according to stimulus rates has been thought to reflect smaller and larger movements (Arnal and Giraud, 2012), indicating that it might be somewhat involved in the prediction of 'what' as well as the prediction of 'when'. Similarly, in the auditory domain, violating expectations (i.e. the omission of a stimulus or a violation of both 'what' and 'when') causes an increase in gamma band power followed by an increase in beta band activity (Fujioka et al., 2009). The increase in beta band activity is likely a result of being updated or corrected by the preceding gamma band activity (Arnal, 2012). An example more closely related to speech is that there is an increase in the beta rebound when the content of predictions about sensory feedback is violated (Arnal et al., 2011). Interestingly, predictive control via the beta band does not appear to be restricted to auditory stimuli as it is also evident in the visual domain (see Bressler and Richter, 2015; Friston et al., 2015). Taken together, these studies show that neural oscillations in the beta band could be utilised to predict both auditory and motor activity. Since top down control by the beta band is evident in a variety of contexts, and because speech production requires

auditory and motor activity, it is possible that this form of prediction might also be used in the context of speech production. In addition, the notion that a frequency associated with motor activity is likely to be implicated in prediction is consistent with the idea that the motor cortex is involved in the generation of such predictive signals (Morillon and Schroeder, 2015).

How does this work in practise? Because the motor system is recruited during perception and production of speech (Morillon et al., 2010; Wilson et al., 2004), it has been theorized that efference copies may be used to anticipate externally generated sensory inputs (Arnal et al., 2011; Arnal, 2012). In particular, motor regions of the brain could exploit low frequency oscillations to make predictions about what sensory feedback will be received and when to move the articulators. Specifically, the basal ganglia must anticipate the completion of the current syllable and anticipate when to move the articulators into the correct position to produce the next syllable in a timely manner (Civier et al., 2013). An ideal candidate for this shifting is the beta band because of its involvement in motor activity and in predicting the content and timing of stimuli. Consistent with this line of reasoning, a recent study (Jenson et al., 2014a), found event related beta desynchronisation during overt (and to a lesser extent, covert) speech. This was thought to reflect predictive coding and specifically the motor cortex sending efference copies to sensory regions. Thus there is empirical evidence for the involvement of the beta band in predicting the timing and content of sensory and somatosensory consequences. When the efference copy reaches the sensory cortices, it is compared with the actual feedback signal (Civier et al., 2013; Hickok, 2012). If there is a difference between the actual and predicted sensory feedback, the resulting error signal is sent back from the sensory cortices to

the motor cortices. A number of groups have indicated this process is mediated via the gamma band. Specifically, gamma is associated with bottom up control and the predictive signalling predictive errors (Arnal 2012; Friston et al. 2015; Wang 2010 see also Fujioka et al. 2009) rather than top-down control. Thus, while the beta band is responsible for predictions and top-down control over sensory regions, the gamma band is responsible for correcting errors and for bottom-up control.

Importantly, the proposed role of oscillations in feedforward and feedback control of speech fits well with existing models of speech production (e.g. Giraud and Poeppel, 2012a; Hickok and Poeppel, 2007; Civier et al., 2013; Fujii and Wan, 2014) which involve a comparison of predicted and actual sensory feedback. Additionally, it is broadly consistent with the speed of error correction. While this has yet to be verified experimentally, this idea expands upon such models through specifying the neurobiological means by which the brain could make such temporal predictions. It further extends the idea of neural oscillations being involved in the perception of speech (Arnal et al., 2011) to the production of speech. In this case, the accurate prediction (of what and/or when) and rapid correction of errors (if they are made) is necessary for fluent speech. It follows therefore that where such prediction (or correction) is inefficient, that speech will be disrupted. The magnitude of the difference between what is observed and what is expected likely corresponds to the extent to which speech is disrupted (see also Civier et al., 2013). Here I suggest that, at the level of the brain, faulty predictive mechanisms may become evident in the phase of low beta band activity and that, conversely faulty error correction, would become evident in the phase of gamma band activity. This idea is supported by evidence from Bidelman (2015). In that study, subjects were asked to assign vowel

sounds as belonging to one of two categories. Beta band activity was enhanced for prototypical rather than ambiguous sounds and Bidelman (2015) concluded that the beta band codes the degree to which (external) speech sounds match internalized phonetic representations for those sounds.

In summary, I have established that 1) both auditory and motor regions are necessary for the fluent production of speech and 2) that the ability to make accurate predictions about incoming stimuli is an essential component of this process and 3) the perception and production of auditory rhythms shares many neural substrates with the predictive mechanisms required for speech production 4) neural oscillations in the beta (and other frequency bands) are particularly important for predicting auditory and motor activity 5) neural oscillations in the beta band may therefore play a very important role in processing the temporal dynamics of speech production. Taken together this evidence suggests that predictive mechanisms (i.e. neural oscillations) used for the perception of rhythms may be qualitatively and quantitatively similar to the mechanisms generating predictions about the current and future states of the articulators. If indeed neural oscillations are necessary for fluent speech production, then the implication is that people with speech disorders should exhibit differences in these frequency bands relative to their fluent peers either during speech or in response to rhythmic tones. A number of authors have implicated rhythm processing problems in some speech disorders (see for example, Alm 2004; for review see Goswami 2015; Tallal et al. 1995; Wieland et al. 2015; Uhlhaas and Singer 2006), but it remains to be seen if such disturbances manifest in the beta and/or other frequency bands. A key challenge for future research, and a major focus of this dissertation, is to determine if there is a relationship between beta band activity and rhythm in

PWS. Additionally, it would be interesting explore how perturbations of the timing and content of auditory feedback modulate beta and gamma activity during speech of PWS and people who don't stutter (PWDS).

Chapter 4

Systematic Review of Neuroimaging Studies of Developmental Stuttering from 1996 to 2015

4.1 Introduction

Stuttering is characterised by involuntary prolongations, repetitions and pauses that disrupt the flow of speech. Stuttering affects 1% of the general population and about twice as many boys as it does girls. While negative effects of stuttering are not generally observed in the first year of onset, those who continue to stutter into adulthood can experience marked disruptions to their quality of life (Boyle, 2015; Gunn et al., 2014; Iverach et al., 2009, 2010) and mental health. Over the last ten years there has been a vast increase in the number of published studies documenting structural and functional differences in the brains of those who stutter compared to their fluent peers (see Figure 4.1). Most of this research has been conducted on AWS. But despite relatively widespread acknowledgement of the need to study CWS (e.g. Busan et al., 2013; Chang et al., 2008; Choo et al., 2011; Cykowski et al., 2010; Cai et al., 2014b; Connally et al., 2014; Cieslak et al., 2015) there have been very few neuroimaging studies of CWS (see for review Chang, 2014). A likely reason for this is because of considerable methodological and practical difficulties associated with acquiring brain-imaging data from children. However, the validity of the conclusions made in light of results from studies of AWS largely rests on the assumption that what is observed in adults generalises to children. This assumption may well be a mistake.

The main aim of this paper is to review the past twenty years of neuroimaging research on developmental stuttering and provide a comprehensive account of the literature.

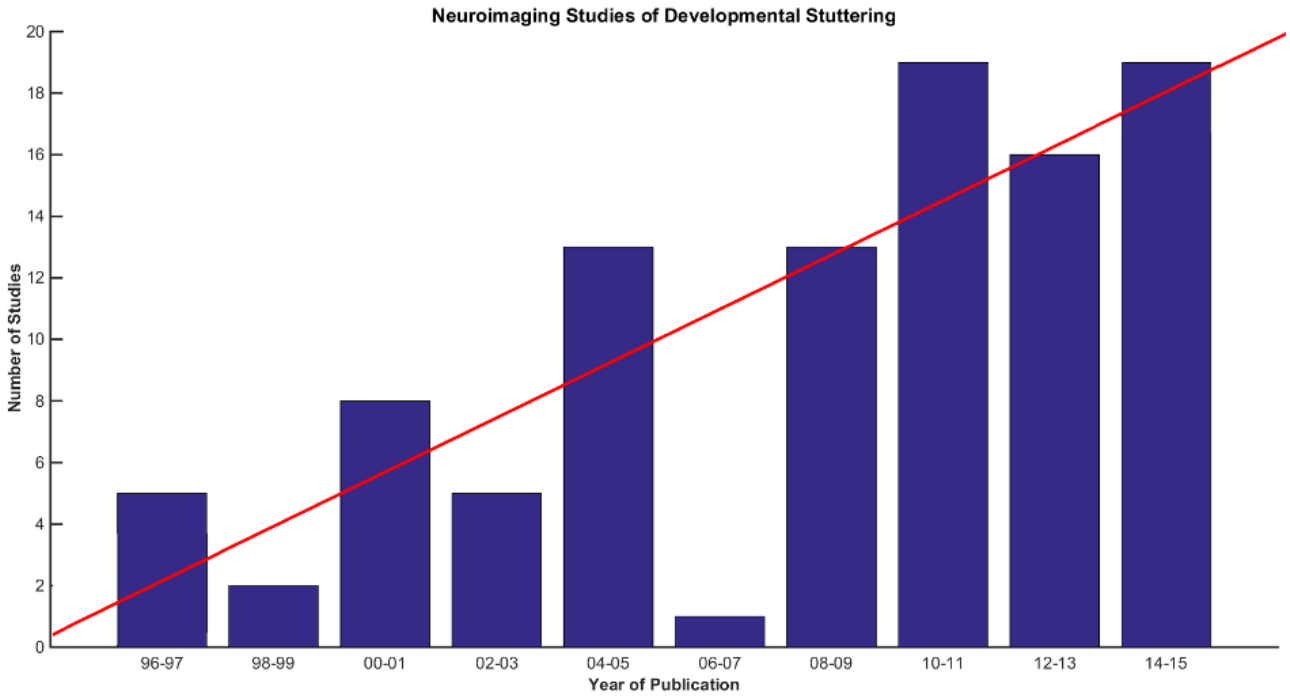

Figure 4.1: Graph of studies on developmental stuttering published between 1996 and 2015. Studies are pooled into two consecutive years (e.g. 1996 and 1997). The red line represents the linear increase in the number of studies published per year.

4.2 Investigating brain structure and function

There are numerous techniques with which to measure the brain in vivo. Each tool provides uniquely different information about the human brain. Diffusion tensor imaging (DTI) measures the direction of water diffusion in the brain and is largely used to assess the structure of the white matter fibre tracts. Additionally, Functional magnetic resonance imaging (fMRI) is an indirect measure of neural activity based on oxygen consumption in the brain. fMRI has a high degree of spatial resolution and is able to measure activity form both cortical and subcortical sources. However, due to the slow evolution of the haemodynamic response, it has relatively poor temporal resolution. Conversely, electroencephalography (EEG) directly measures cortical activity from the scalp. It has a high degree of temporal resolution, in the order of milliseconds, but due to the way electrical fields are conducted from the brain to the scalp, has a low degree of spatial resolution. Near infrared spectroscopy (NIRS) is a tool used to measure concentrations of haemoglobin in cortical regions of the brain from the scalp. Compared to magnetic resonance imaging (MRI), it is relatively cheap and easy to set up but is limited to investigation of neural activity in the cortical surface. Magentoencephalography (MEG) is another direct measure of neural activity and detects the magnetic fields that are perpendicular to the electrical fields generated by the brain. Like EEG, MEG also has a high degree of temporal resolution, but owing to the fact that magnetic fields do not take the path of least resistance when exiting the brain it has a higher degree of spatial resolution. Although not as accurate as fMRI, MEG has been reported to detect activity from subcortical sources (e.g. Fujioka et al., 2010; Ng et al., 2013). Neu-

rostimulation methods such as transcranial magnetic or electric stimulation (TMS and TES respectively), are uniquely the only techniques that can be used to induce transient virtual lesions, manipulate and measure cortical excitability or inhibition and manipulate communication at or between cortical regions of the brain.

4.3 Systematic Review

The studies included in this review were obtained by an extensive search of Google Scholar using terms 'stuttering' AND 'adults' OR 'children' between 1996 and 2015. I only included studies using some form of neuroimaging (f/MRI, PET, DTI, NIRS), neurophysiology (MEG and EEG) or neuro-stimulation, (TMS/TDCS). I broadened these criteria (to 'stuttering' AND 'brain') in order to detect publications that did not include the primary keywords or that were missed by our earlier search. Only peer reviewed journal articles were included (i.e. abstracts (Rastatter et al., 1998), book chapters (Bowyer and Peacock, 2014) or unpublished doctoral or masters theses (Song et al., 2007) were excluded). I also excluded studies on acquired or neurogenic stuttering (e.g. Vanhoutte et al., 2014), case studies on developmental stuttering (e.g. Sowman et al., 2012), those that administered pharmacological agents to induce or ameliorate stuttering (e.g. Tykalová et al., 2015) or those that only detailed neuro-computational models of stuttering (Civier et al., 2013).

For ease of reading, I have separated the studies into a number of categories: 1) structural studies 2) functional neuroimaging/neurophysiological studies of speech (i.e. fMRI and M/EEG studies, 3) TMS and EEG (non-speech) studies and 4) miscellaneous studies which do not fit neatly into the other categories. I wish to

emphasise that these categories are not mutually exclusive but rather simply placed into a category based on what appeared to be the most relevant focus of that study for ease of reading and reference for the reader. For a summary of important details of the neuroimaging studies on AWS such as the methodology, number of participants, task and main findings, see Appendix A. For a summary of the same details on studies of CWS, see Appendix B. The studies that recruit both AWS and CWS but do not specifically focus either group are presented in Appendix C.

4.3.1 Structural Abnormalities

There have been eight studies investigating brain structure using voxel based morphometry in stuttering (Beal et al., 2007, 2013; Cykowski et al., 2008; Jäncke et al., 2004; Kell et al., 2009; Kikuchi et al., 2011; Lu et al., 2010b; Choo et al., 2011, 2012). Of those studies, 3 specifically focused on CWS (Beal et al., 2013, 2010; Choo et al., 2012). Similarly, a total of twelve studies have investigated brain structure using DTI or fibre tracking in stuttering (Cai et al., 2014b; Chang et al., 2008, 2011; Chang and Zhu, 2013; Chang et al., 2015; Connally et al., 2014; Cykowski et al., 2010; Civier et al., 2015; Kronfeld-Duenias et al., 2014; Mock et al., 2012; Sommer et al., 2002; Watkins et al., 2008) and five others focused on volumetric MRI (Beal et al., 2015; Foundas et al., 2001, 2003, 2004, 2013). Of those, 4 have specifically focused on CWS.

Perhaps the most consistent finding over the past ten years of research is that both AWS and CWS exhibit a reduction in fractional anisotropy - a measure of white matter integrity - in the left rolandic operculum and its surrounding areas (Chang

et al., 2008, 2015; Connally et al., 2014; Cykowski et al., 2010; Sommer et al., 2002; Watkins et al., 2008). The left rolandic operculum - sometimes referred to as the inferior frontal gyrus - is in close proximity to the speech motor representations of the tongue, larynx and pharynx as well as the arcuate fascicle (Sommer et al., 2002). A reduction in the white matter underlying this region could affect the neural processes associated with the planning and execution of speech. Some of these decreases in white matter are driven by greater rather than normal radial diffusivity (Cykowski et al., 2010). Increases in radial diffusivity (diffusion of water perpendicular to the main direction of axon bundles) are thought to index disruptions in white matter integrity. The white matter deficits observed in studies of stuttering are prevalent in motor and auditory areas. AWS and CWS show reduced white matter integrity in the ventral premotor cortex (Connally et al., 2014; Watkins et al., 2008; Chang et al., 2015) as well as a bilateral reduction of white matter in the forceps minor of the corpus callosum (Beal et al., 2013; Civier et al., 2015; Connally et al., 2014) and in the left superior temporal gyrus (Chang et al., 2015; Lu et al., 2010b). CWS were also observed to have atypical brain torque as compared to CWDS (Mock et al., 2012).

The observation of common abnormalities between AWS and CWS is important to consider because it could point to a biomarker of stuttering. Chang et al. (2015) showed that CWS exhibit increased fractional anisotropy in the cerebellum which they noted was associated with the organisation of sequential movements into chunks (e.g. Sakai et al., 2004). The reason why such differences are evident at such a very early age (3-10 years old) likely has implications for the acquisition of speech and perhaps even the timing of speech (Smits-Bandstra and Luc, 2007). Structural

abnormalities have been observed in auditory regions of the brain. The left planum temporale is larger than the right planum temporale in AWDS but not in AWS. In AWS, the two regions are generally the same size (Foundas et al., 2001, 2004). Interestingly, these authors suggested that stuttering could be considered a 'momentary instability when the timing between linguistic and phonatory loops are disrupted'. Similarly, Jäncke et al. (2004) identified a leftward bias in white matter volume of the auditory cortex in AWS but not in AWDS. These authors also found increased white matter in the right inferior frontal cortex, superior temporal gyrus (including planum temporale) and the precentral gyrus in AWS relative to AWDS and suggested their findings related to atypical intrahemispheric communication.

It is not just specific regions of the brain that have been found to be different between stutterers and their fluent peers, but also the anatomical connections between them. Recent work by Neef et al. (2015a) conducted a meta analysis of several DTI studies of stuttering. This identified three clusters of voxels that significantly differed between AWS and AWDS. These are: the left superior longitudinal fasciculus, a cluster in the the left central sulcus (also part of the superior longitudinal fasciculus) and a third cluster in the posterior mid body of the corpus callosum. This third cluster was found to connect sensorimotor regions.

The arcuate fasciculus connects Broca's and Wernike's areas (Rilling et al., 2008) and plays a major role in speech production. This tract is reduced in its integrity in AWS (Connally et al., 2014; Watkins et al., 2008) and CWS (Chang et al., 2008, 2015) relative to matched controls. Interestingly, recent work by Cieslak et al. (2015) revealed that large portions of this tract were completely absent in

AWS relative to AWDS. Kronfeld-Duenias et al. (2014) found that the anatomical connection between the SMA and the inferior frontal gyrus - the frontal aslant tract (see Catani et al., 2013) - is abnormal in AWS as evidenced by increased levels of mean diffusivity. That there were differences in the level of mean diffusivity not accompanied by differences in fractional anisotropy imply that there are fewer constraints on diffusion that are not specific to any direction. Notably, Kronfeld-Duenias et al. (2014) recorded that mean diffusivity in this tract was correlated with decreased speech fluency and speech rate in AWS. This tract has an important role in speech production as evidenced by the fact that electrically stimulating it leads to speech arrest (e.g. Vassal et al., 2014) in much the same way that electrical stimulation or TMS of Broca's area does (Devlin and Watkins, 2007). The frontal aslant tract therefore is functionally relevant for speech, though little is understood about its significance in the aetiology of stuttering. Furthermore, while this tract has not yet been investigated in CWS, those groups that do have the requisite data could reanalyse their datasets to make such a comparison.

The one study that has examined white matter connectivity in CWS focused on connections within the basal ganglia thalamocortcial loop. Chang and Zhu (2013) documented that CWS had reduced connectivity from the putamen to the left inferior frontal gyrus. CWS also had reduced connectivity from the left SMA to several cortical areas including the bilateral precuneus, thalamus, cingulate nucleus, the left precentral gyrus and putamen, right inferior and middle frontal and fusiform gyrus, caudate and insula. CWDS exhibit greater connectivity from the inferior frontal gyrus to temporal areas and subcortical regions like the putamen compared to CWS. Finally, CWS also had reduced connectivity from the left superior temporal gyrus

to the left insula, caudate, right cerebellum and bilateral putamen. Furthermore, these findings parallel a report by Beal et al. (2013) who found reduced grey matter volume in the left putamen on CWS and a study by Lu et al. (2010b,a) who found widespread differences in structural connectivity between AWS and AWDS. They found decreases in connectivity between left motor cortex to the pars opercularis in boys but not girls perhaps indicates this region is important for recovery from stuttering (as more girls than boys recover from stuttering).

A well known characteristic of grey matter is that it changes in response to experience. Repeated use of a brain regions often results in expansion of that area whereas under utilising a brain region can lead to a decrease in its size. For example musicians have increased hand motor representation in the brain (see for review Herholz and Zatorre, 2012; Lappe et al., 2008). For this reason, some authors (e.g. Beal et al., 2013; Lu et al., 2010b) have suggested that the structural changes and increased number of gryri (Cykowski et al., 2008) observed in AWS are likely to be the result of continued struggles with stuttering. In a similar vein, it has been asserted that the abnormal structure/function in the right hemisphere in stuttering is a direct result of abnormal structure and functioning of the left hemisphere (Chang et al., 2011; Choo et al., 2011). For example, deficits in the left superior temporal gyrus may result in increased reliance on the right hemisphere homologue (Kikuchi et al., 2011). grey matter volume increases in the left inferior frontal gyrus, bilateral precentral gyrus and the left putamen of AWS (e.g. Beal et al., 2007; Lu et al., 2010b) may perhaps be the result of (adaptive or maladaptive) compensation. The putamen (Beal et al., 2013; Chang et al., 2008) and caudate (Foundas et al., 2013) show reduced grey matter volume in CWS, perhaps reflecting the fact that they are

under-utilised, not utilised efficiently enough or did not develop properly in the first place. Nevertheless, there are also some areas such as the bilateral medial frontal gyrus that exhibit decreased grey matter volume in both AWS and CWS (Lu et al., 2010a; Chang et al., 2008) and the right superior temporal gyrus which exhibits increased grey matter volume in AWS (Beal et al., 2007) and CWS (Beal et al., 2013). Many of the sites in the brains of PWS where there are structural differences also exhibit functional activation abnormalities. (see below).

4.3.2 Functional MRI and PET studies of stuttering

The majority of neuroimaging or neurophysiological studies examining differences between stuttering and non-stuttering individuals have focused explicitly on speech production. 8 studies have used Positron Emission Tomography (PET) (Braun et al., 1997; DeNil et al., 2000, 2001; Fox et al., 1996, 2000; Ingham et al., 2004, 2012, 2013) and 17 have used fMRI (Chang et al., 2009; Giraud et al., 2008; Howell et al., 2012; Kell et al., 2009; Loucks et al., 2011; Lu et al., 2009, 2010b,a; DeNil et al., 2008; Neumann et al., 2004, 2005; Preibisch et al., 2003; Sakai et al., 2009; Toyomura et al., 2011, 2015; Van Borsel et al., 2003; Watkins et al., 2008). For the most part, they have revealed differences in neural activity throughout cortical and subcortical regions and in the functional connections between them. Although these distinctions are not mutually exclusive, I will discuss each of them in turn.

The very fact that neural activation is often compared between PWS and PWDS during speech implies that researchers expect there to be basic neural differences in how the groups produce speech. More specifically, it suggests there will be

certain patterns of abnormal neural activation evident in PWS even when they are fluent. The fluent speech of PWS is perhaps very different from dysfluent speech. Such activity has recently been described in three separate meta-analyses (Brown et al., 2005; Belyk et al., 2015; Budde et al., 2014) which included a number of the studies listed above. These authors reported that fluent speech of AWS was characterised by an under activation of the left auditory cortex and the left laryngeal motor cortex as well as overactivations in the right inferior frontal gyrus and the pre-SMA. Despite several groups asserting the involvement of the basal ganglia in stuttering, Belyk et al. (2015) did not detect any reliable activation in the area. This highlights the possibility that the basal ganglia is not involved in stuttering. However, the variable size of the structure may contribute to its apparent lack of activation across studies (Civier et al., 2013). However, the fact that the basal ganglia activation was not reported across several studies is not grounds for dismissing its involvement in stuttering. Additionally, Belyk et al. (2015) did report activation of the SMA which is a major output of the basal ganglia. Notably, this region is also implicated in the pathological basis of stuttering (Packman et al., 2007).

Several more recent studies have reported abnormal activation of the basal ganglia across various speech tasks (Chang et al., 2009; Kell et al., 2009; Toyomura et al., 2011; Watkins et al., 2008). While functional activations detected by meta analysis (Belyk et al., 2015; Budde et al., 2014) are relatively stable across studies, it is unknown whether they are neural signatures related to the cause of stuttering or are the result of having stuttered for a number of years. To have some idea about the functional activations associated with the cause of stuttering it is necessary to study CWS as they are close to the age of stuttering onset and are less likely to be

affected by compensatory neural reorganisation. To the best of our knowledge only one study has looked at functional connectivity in CWS (see Chang and Zhu, 2013). This perhaps suggests that the abnormalities in stuttering may extend beyond the domain of speech and affect the motor system more generally. Studying the brain activations associated with normal speech production provides valuable information about the locations of abnormalities; studying speech under conditions that induce fluency in dysfluent individuals can also provide valuable insights into the brain basis of stuttering and how fluency might be attained.

Fluency can be induced under a variety of conditions such as choral speech, speaking in time with a metronome, under delayed auditory feedback or after therapy. Theoretically, fluency can be induced for a number of reasons: either because they restore normal speech functioning to impaired areas, because they increase reliance on compensatory neural mechanisms or alternatively some combination thereof. The patterns of neural activation associated with fluency inducing conditions and speech therapy could establish the most effective neural correlates of inducing fluency. Speech therapy has widespread effects on brain activation in AWS. Following therapy, AWS show reduced right hemispheric activation (Neumann et al. 2004, though see Kell et al. 2009 for the reverse finding), reduced hemisphere cerebellar activation (DeNil et al., 2001; De Nil et al., 2004; Lu et al., 2012; Toyomura et al., 2015), increases in left hemispheric activation in the inferior frontal and precentral gyrus (De Nil et al., 2004; Neumann et al., 2004) and increased basal ganglia activity (Ingham et al. 2013; Neumann et al. 2004; Toyomura et al. 2015 and see also Giraud et al. 2008) compared to pre-treatment activations. Interestingly, DeNil et al. (2001) found that while activation in regions like the cerebellum persist up to

1-2 years after therapy, activation in the putamen does not. Nevertheless, it has been reported that the level of activation in the putamen is a predictor of the likelihood of successful or unsuccessful treatment (Ingham et al., 2013). Lu et al. (2012) reported that the left levels of activation in the inferior frontal gyrus did not change following treatment. This was taken to suggest that the left inferior frontal gyrus was the pathological basis of stuttering (see also Neumann et al. 2004) and Kell et al. 2009 for a similar view). Because there are structural and functional deficits in the inferior frontal gyrus, but only functional deficits in the basal ganglia, the latter is perhaps secondary to those in the inferior frontal gyrus.

During choral reading there is a reduction in the overactivation of the cerebellum, SMA. There are inconsistent findings with respect to the basal ganglia: Fox et al. (1996) reported a decrease in globus palladus during choral reading, but others have suggested that activation still remains less than that of controls (Toyomura et al. 2011 and see also Wu et al. 1995). These reductions are correlated with increased fluency in AWS (Fox et al., 2000). Toyomura et al. (2011) attributed the persistent low level of activation in the basal ganglia as because AWS were not required to generate their own prosodic rhythm and integrate it with speech. Interestingly, Himberg et al. (2015) showed that behaviourally there is a high degree of coherence in the duration of the inter-word interval of subjects asked to contribute alternating words to construct a story. This suggested that when speaking in time with someone else it is relatively easy to speak at the appropriate time. The main neural commonality between fluency inducing conditions is that choral speech (Fox et al., 1996; Ingham et al., 2004; Wu et al., 1995), metronome timed speech (Braun et al., 1997; Stager et al., 2004; Toyomura et al., 2011), singing (Stager et al., 2004) and delayed auditory

feedback (Watkins et al., 2008; Sakai et al., 2009) all raise activity in the auditory areas in AWS. The increased activation of auditory areas is hard to reconcile with the idea that they cause fluency as a result of decreasing attention to vocal output. If this were occurring then it would perhaps cause a decrease in activation of auditory areas. A more plausible explanation is that the increased activation reflects efficient integration of auditory information for the purposes of speech production. Notably, many of the brain areas engaged during fluency inducing conditions are also those associated with the timing and sequencing of movement.

4.3.3 Functional Connectivity

Whereas prior to 2005 neuroimaging research into stuttering tended to focus on differences in localised functional activation, later work has tended to focus on functional (and structural) connectivity between brain areas. Such studies include (Chang et al., 2009; Howell et al., 2012; Lu et al., 2009, 2010b) and (Lu et al., 2010a). AWDS exhibit a normal pattern of functional connectivity during speech tasks in contrast, AWS do not show the same patterns of functional connectivity or show evidence of additional connections that are not existent in AWDS. For example, whereas AWDS had a connection from the left inferior frontal gyrus to the left precentral gyrus, AWS did not (Lu et al., 2010a). In addition, AWS exhibited abnormalities in the connections between the left superior temporal gyrus and the putamen. AWS also were found to have a connection between the right putamen and the SMA, that was not present in AWDS. This led the authors to conclude that it is difficult for the basal ganglia to provide timing cues for speech (see also Alm, 2004; Etchell et al.,

2014a). Interestingly, Lu et al. (2010a) argued that the connection between the left superior temporal gyrus and the putamen may exacerbate the functioning of areas like the SMA and the left inferior frontal gyrus.

Chang et al. (2011) found that AWS exhibited weaker functional connectivity compared to AWDS between the left inferior frontal gyrus and the premotor cortex superior temporal gyrus. AWS also showed greater connectivity between the left BA (Brodmann Area) 44 and the right postcentral gyrus, left anterior cingulate cortex and left anterior cingulate during speech and non speech tasks. Howell et al. (2012) found that AWDS exhibited significant connections between the left laryngeal motor cortex and the left insula. In contrast to this, AWS showed a connection from the left laryngeal motor cortex to the putamen. Lu et al. (2010b) found AWS had weaker connections from the middle temporal gyrus to the putamen, and stronger connectivity from the putamen to the thalamus and from the thalamus to the SMA. A later study by the same group found that the connections between bilateral inferior frontal gyrus and the right putamen contributed most to planning of speech. In contrast to this, the premotor cortex and cerebellum contributed most to production (Lu et al. 2010a, see Chang et al. 2009 for an fMRI study also separating planning and execution of speech). Lu et al. (2010a) suggested that the right inferior frontal gyrus would have a greater role in planning than in execution and drew particular attention to the angular gyrus as the interface between planning and execution. These findings suggest that there are distinct patterns of activation associated with abnormalities in planning and execution of speech in AWS relative to AWDS, which helped to clarify some inconsistent reports between studies. Many of the patterns of functional connectivity identified in these studies are consistent with previous reports

of abnormal structure in cortical and subcortical areas.

Overall, functional neuroimaging studies of speech production using MRI and PET have documented widespread differences in activation and connectivity between sensory and motor regions of the brain in AWS and AWDS. While both of these techniques have exquisite spatial resolution, they lack the temporal resolution necessary to describe the fast paced neural dynamics associated with speech production.

4.3.4 M/EEG Studies of AWS/CWS

The most common methods of acquiring information about the timing of brain activations are EEG and MEG. There have been 8 MEG studies of AWS/CWS (Beal et al., 2010, 2011; Biermann-Ruben et al., 2005; Kikuchi et al., 2011; Salmelin et al., 1998, 2000; Sowman et al., 2014; Walla et al., 2004). Two of these studies have focused on children (Beal et al., 2011; Sowman et al., 2014). There have been fifteen EEG studies relating to speech production and auditory processing in stuttering (Achim et al., 2008; Arnstein et al., 2011; Corbera et al., 2005; Daliri and Max, 2015; Hampton and Weber-Fox, 2008; Jansson-Verkasalo et al., 2014; Kaganovich et al., 2010; Liotti et al., 2010; Mock et al., 2015; Morgan et al., 1997; Özge et al., 2004; Özcan et al., 2009; Rastatter et al., 1998; Sassi et al., 2011; Vanhoutte et al., 2015; Weber-Fox et al., 2004).

The first MEG study of stuttering examined neural responses to tones presented while subjects were speaking or reading (Salmelin et al., 1998). While the timing of evoked responses from dipoles in the auditory cortices were similar, the amplitude of the M100 response, thought to index a decrease in neurons available to

process sounds was larger in AWS relative to AWDS. The amplitude of the M100 was larger in the left than right hemisphere. A later study by the same group (Salmelin et al., 2000) tested the effects of single word reading on brain activation in stuttering. These authors found that, whereas neural activations in AWDS progressed from the left inferior frontal cortex (involved in articulatory planning) to the left frontal parietal cortex and then to the motor cortex, AWS showed a reversed pattern where activation progressed from the frontal parietal cortex to the left inferior frontal cortex. These findings were thought to reflect disordered generation of motor programs before the completion of articulatory planning contributed to stuttering. Salmelin et al. (2000) observed suppression of the beta band oscillations (a 20 Hz rhythm usually associated with movement) in the mouth area of the motor cortex in AWDS, but in both the mouth and hand area of the cortex of AWS. This finding suggests that stuttering is a general motor control disorder (see TMS studies below) because the abnormal beta oscillatory response is normally limited to the mouth representation of the motor cortex. A few other studies have investigated beta band suppression in AWS and CWS. For example, Rastatter et al. (1998) demonstrated that the beta band (traditionally associated with motor activity) was significantly greater in AWS than AWDS and this excessive activity was reduced by delayed and frequency altered feedback of speech. Özge et al. (2004) found reduced beta band activity during breathing and hyperventilation in CWS as compared to CWDS. AWS and CWS exhibit substantial differences in movement related activity relative to their fluent peers.

There is growing evidence that AWS have abnormalities in not only the neural processes associated with movement, but also the neural processes associated with

the preparation to move. One measure of movement preparation is the contingent negative variation. The contingent negative variation is a slow wave measured in either EEG or MEG preceding the onset of movement. Achim et al. (2008) found that this component was smaller in AWS than AWDS during both stuttered and fluent speech indicating that AWS were less prepared for the production of the articulatory movement. Later, Vanhoutte et al. (2015) reported that during the production of single words, the slope of the contingent negative variation was steeper in AWS than in AWDS and positively correlated with stuttering severity. This suggested AWS have increased motor preparation as a result of dysfunction in the basal ganglia thalamo-cortical loop. However, it is also possible that the increased amplitude reflects greater effort to achieve the same degree of motor readiness. In other words, AWS might actually be less prepared to move and require a greater degree of preparation to execute the planned movement. The authors attributed the increased motor readiness to dysfunction in the basal ganglia thalamo-cortical loop. This idea is broadly in line with the involvement of the basal ganglia in the generation of the contingent negative variation (Bares and Rektor, 2001) and fits with the hypothesis that the structure is associated with stuttering.

Daliri and Max (2015) investigated speech planning by examining auditory evoked responses to tones presented prior to speaking or silent reading of a word or seeing a string of fixation crosses. Whereas the AWDS showed a reduction in the amplitude of the N100 response on the tone trials relative to the control conditions, AWS did not. This was taken to suggest that AWS have difficulty in predictively modulating sensory systems prior to speech. These neural responses are broadly consistent with an MEG study by Walla et al. (2004) who found that, whilst AWDS

exhibited a Bereitschaft potential, brain activity -50ms prior to the onset of speech in a region close to the motor cortex, AWS did not. This was thought to indicate that AWS lacked a state of 'focused verbal anticipation' that is linked to gathering and preparing information required to actually produce a word. The lack of preparatory activity is perhaps also linked with decreases in cortical excitability in AWS relative to AWDS (see TMS studies below). Reduced motor preparation may be a cause, consequence or symptom of reduced excitability in the motor cortex. This could in turn affect the initiation of movements such as speech. More recently, Mock et al. (2015) presented subjects with a tone while they were preparing to speak. Subjects were presented with a cue that either allowed them to prepare to name the target, or a cue that did not allow them to prepare to name the target. The subjects heard a tone between the cue and the target and the electrophysiological response was thought to index an efference copy (motor cortex sending copies of motor commands to sensory regions). Mock et al. (2015) found a significantly reduced amplitude of the N100 in AWS compared to AWDS suggesting that efference copy might be impaired in AWS.

Biermann-Ruben et al. (2005) examined the temporal dynamics of cortical activation during sentence reading in AWS and AWDS. Notably this was considerably more complex than the studies above as it involved the production of a sentence rather than one isolated word. AWS but not AWDS exhibited activation in the left inferior frontal cortex between 95 and 145ms relative to the onset of speech. AWS also engaged the right frontal operculum and this was taken to indicate abberant hemispheric dominance. A later study by Sowman et al. (2014) examined the hemispheric laterality of CWS and CWDS during speech production (picture naming).

These authors found no difference between groups suggesting that abnormal laterality is something that develops after having stuttered for a long period of time (e.g. Foundas et al., 2013). Notably, this later finding is consistent with the presence and absence of differences in white matter of the corpus callosum in AWS (Choo et al., 2011) and CWS (Choo et al., 2012) respectively.

Beal et al. (2010, 2011) examined the phenomenon of speech induced auditory suppression, the suppression of auditory activity that occurs when a person speaks relative to when they listen to the same sound. In both studies, the amount of suppression in PWS was remarkably similar to the suppression observed in PWDS. There was however a delay in the M100 component in AWS relative to AWDS and a delay in the M50 component for CWS relative to CWDS, suggesting that auditory processing was slower. The observation of similar amplitude but delayed latency of speech induced suppression, has been replicated by at least one other EEG study (Liotti et al., 2010) in AWS compared to AWDS. Arnstein et al. (2011) investigated error-monitoring processes during a task where they had to judge whether or not a 'target' was orthographically similar, dissimilar and rhymed or did not rhyme with a 'test' word. Responses were made via a button press and errors were indexed by the error related negativity (an electrophysiological component that peaks about 100ms after an incorrect response) and the error related positivity (another component that peaks 200-400ms after an incorrect response). For example an error related negativity and error related positivity could be observed when judging that a target word rhymed with a test word when, in fact, it did not. Findings indicated that excessive error monitoring could lead to dysfluencies by disrupting speech (planning). To test this, Arnstein et al. (2011) gave AWS a 'target' word and then present them

with 'test' words. In accordance with their hypothesis, AWS showed a large error related negativity regardless of the accuracy of their response. This suggested that AWS perceive their speech plan as being incorrect, even when there is nothing wrong, and that the resulting attempts to repair speech cause stuttering. A similar paradigm was used by Weber-Fox et al. (2004) and showed that AWS exhibit poorer judgement of whether target and test words rhyme. AWS also showed a greater peak amplitude of the difference between the rhyming judgements and baseline task in the right hemisphere, but not in the left hemisphere. In comparison, the amplitude of the difference components was similar across hemispheres for the AWDS. The general similarity in evoked responses between AWS and AWDS in response to judgement tasks led the authors to conclude that core neurophysiological deficit in stuttering did not relate to phonological deficits.

The final study to use MEG to examine neurophysiological responses in AWS did not focus on speech production, but rather on the auditory processing abilities of AWS. Kikuchi et al. (2011) assessed the abilities of AWS and AWDS to gate out (i.e. ignore) the second of two sequential stimuli. Whereas AWDS exhibited a suppression of the M100 response, AWS did not and this was taken to suggest AWS have difficulties in suppressing irrelevant sensory input. This was in contrast to a previous EEG study (Özcan et al., 2009) which found no difference in P50 suppression between CWS and CWDS. These discrepancies could be attributed to differences in methodology: MEG is more sensitive to tangential sources and EEG to both radial and tangential sources because MEG measures magnetic fields that occur perpendicular to the electrical fields generated by the brain. Abnormalities in sensory gating may develop with continued stuttering rather than being present

at its onset. Indeed, most studies of AWS show no differences in the timing or amplitude of EEG responses to oddball tones or pure tones compared to AWDS (Biermann-Ruben et al., 2005; Hampton and Weber-Fox, 2008; Sassi et al., 2011).

Morgan et al. (1997) recorded ERPs from two electrodes (C3 and C4 according to the international 10-20 system) over the left and right hemispheres, and found that AWDS show an increased right hemisphere amplitude of the P300 component as compared to the left hemisphere but that there is no such asymmetry in AWS, a result which was interpreted as evidence for altered cerebral dominance in stuttering. Similarly, Corbera et al. (2005) examined MMN responses to tones and phonetic contrasts. Canonically, MMN responses refer to the difference between the evoked response to a frequently presented stimuli (the standard) and an infrequently presented stimuli (the deviant). The standard and the deviant tones generally differ in one characteristic such as frequency, duration, or volume and the neural response is an index of how well an individual is able to detect a change. Corbera et al. (2005) found that AWS showed normal MMN responses to tones, but more left lateralized MMN responses to phonetic contrasts relative to AWDS. Similarly, AWS and CWS show abnormal auditory evoked brainstem responses to tones (Khedr et al., 2000; Tahaei et al., 2014). Additionally, while frequent 1KhZ tones elicit similar neural responses in AWS and AWDS, rare 2kHz tones elicit a P300 response in CWDS but not in CWS (Kaganovich et al., 2010). Work by Jansson-Verkasalo et al. (2014)) has demonstrated that CWS show a MMN response to changes in duration of vowels, but not to other linguistic features such as intensity or frequency, which do elicit a MMN response in CWDS. Sassi et al. (2011) found no significant difference in the amplitude or latency of the P300 to rare tones before or after speech therapy for

stuttering suggesting that auditory processing was not a major issue in stuttering. It may, however, be the case that neural responses to unexpected changes in tone frequency cannot reliably differentiate between AWS and AWDS.

Together, M/EEG studies of speech production show that AWS and CWS differ markedly from their fluent peers in terms of the temporal order of activation across brain regions, in the neural markers of speech preparation and in error monitoring during speech. Many of these differences in brain activation occur within one second of stimulus or speech onset. There is also conflicting evidence for impaired auditory processing in response to pure tones in stuttering. Some studies show there is an impairment when listening to tones but others do not (e.g. Biermann-Ruben et al., 2005; Sassi et al., 2011).

4.3.5 EEG Studies of Psycholinguistics in stuttering

In addition to those EEG studies mentioned in the preceding paragraph, there have been a number that have largely focused on syntactic processing or the psycholinguistic properties of words. These include a total of ten studies (Arnstein et al., 2011; Cuadrado and Weber-Fox, 2003; Maxfield et al., 2010, 2012, 2015; Usler and Weber-Fox, 2015; Weber-Fox, 2001; Weber-Fox et al., 2008; Weber-Fox and Hampton, 2008; Weber-Fox et al., 2013). Verb agreement violations elicit a P600 in both AWDS and AWS, but this peak is significantly reduced and less distributed in AWS than in their fluent peers (Cuadrado and Weber-Fox, 2003). When listening to sentences containing verbs that were appropriate for the context, but syntactically incorrect (e.g. 'Every day the children pretends to be superheroes'), AWS but not AWDS show

an increase in the N400 amplitude (Weber-Fox et al., 2008), which was interpreted as reflecting greater processing difficulty. The same N400 component appears to be delayed in CWS relative to their fluent peers when judging whether a target word rhythms with a prime word (Weber-Fox and Hampton, 2008) and when listening to semantic violations (Weber-Fox et al. 2013, though see Weber-Fox 2001 for reduced N400 amplitudes in AWS). This appears to be a relatively stable finding because a number of other studies have also identified abnormalities in the N400 response in stuttering. Semantically (and phonologically) related words reduce the amplitude of the N400 response in AWDS but increase the amplitude of the N400 response in AWS (Maxfield et al., 2010, 2012). It suggests that while priming can facilitate speech production in AWDS, the same stimulus leads AWS to actively inhibiting competition to the prime, thereby making access to a semantically related probe more difficult. Interestingly, the N400 component may distinguish between children who have recovered from stuttering and persistent CWS (see Usler and Weber-Fox, 2015). A later study, Maxfield et al. (2015) examined the neural processes immediately before speech production. This study showed that AWS but not AWDS showed a P280 component sensitive to (identity) priming. This was taken to suggest that the AWS had more focused attention immediately prior to speech production.

4.3.6 TMS Studies

While the spatial and temporal dynamics of speech production can be readily examined with fMRI, PET, MEG and EEG, neurophysiological techniques like TMS are unique because they allow probing of the excitation and inhibition of cortical

regions. There have been a total of eight studies that have used TMS (Alm et al., 2013; Busan et al., 2013; Neef et al., 2011a,b, 2015b; Sommer et al., 2003, 2009) to compare cortical excitability and inhibition between AWS and AWDS.

The earliest studies (Sommer et al., 2003, 2009) compared interhemispheric inhibition between AWS and AWDS. Recording activity from the abductus digitis minimi, Sommer et al. (2009) found that there was no significant difference between groups with respect to the amplitude of the conditioned motor evoked potentials (MEPs). This suggested that interhemispheric inhibition was normal in AWS, a result that is consistent with their previous studies (Sommer et al., 2003). These authors also found an elevated motor threshold, a measure of cortical excitability in AWS relative to AWDS. Alm et al. (2013) compared the side-to-side difference in motor threshold revealing that AWS have an elevated motor threshold in left hemisphere relative to their own right hemisphere and to the left hemisphere of AWDS. Further TMS work in the same year by Busan et al. (2013) demonstrated that AWS exhibit a reduced MEP amplitude in the left hemisphere compared to AWDS. Together these studies suggest that stuttering may be a symptom of a broader motor control disorder because there is abnormal excitability in the hand representation of the motor cortex as well as the mouth representation of the motor cortex. This work is broadly consistent with Salmelin et al. (2000) observation of spreading of neural activity from the mouth to the hand representation in AWS during speech.

Until the last few years, most TMS studies of stuttering focused on the hand motor representation of the brain because it was deemed too hard to record from orofacial muscles like the tongue. However, Neef et al. (2011a) showed that AWS

have reduced short intracortical inhibition and intracortical facilitation in the tongue representation of the motor cortex. This highlighted abnormalities in the excitation and inhibition in AWS relative to AWDS in an area crucially involved in articulation when at rest. The lack of excitability may underpin a level of activity during speech. More recently, Neef et al. (2015b) examined the active motor threshold of AWS and AWDS while they were generating a verb. AWS seemed to exhibit less excitability (i.e. higher motor thresholds) than AWDS in the tongue representation of the motor cortex in both the left and right hemispheres of the brain. Additionally, AWS failed to show an increase in excitability (MEP amplitude) prior to movement that was seen in AWDS up to 160ms before speech onset that was evident in AWDS. Importantly, this study directly linked observations of decreased cortical excitability to speech production. By demonstrating reduced excitability of the motor cortex during speech, Neef et al. (2015b) show that alterations in excitability could indeed impact speech production. This parallels observations of reduced functional activation in the left motor regions.

Another study by the same group explored the idea that stuttering was related to deficits in timing (Neef et al., 2011b). These authors applied repetitive TMS to the left and right dorsal premotor cortex of AWS and AWDS and examined the effects on behavioural performance during a paced finger tapping task. In AWDS, repetitive TMS of the left dorsal premotor cortex impaired tap to tone asynchrony in the left but not the right hand. Conversely, in AWS, repetitive TMS of the right dorsal premotor cortex impaired the tap to tone asynchrony when tapping with the left hand. This suggests that timing control in AWDS is mediated by the left hemisphere but that it is shifted to the right hemisphere in AWS. These findings are

generally consistent with rightward shifts in motor and premotor activations in AWS (e.g. Braun et al. (1997); Fox et al. (2000)) but also highlight impaired predictions in AWS (see Pollok et al. (2009)). Neef et al. (2011b) is the only study I am aware of to apply repetitive TMS in a study of AWS. Given knowledge about cortical areas involved in stuttering it would be interesting to investigate whether repetitive TMS can induce stuttering like dysfluencies in AWDS. If TMS could induce stuttering like dysfluencies then it could provide a causal link between stuttering and the cortical region being stimulated.

Collectively, the observation of increased motor thresholds and decreased cortical excitability suggest the difficulty AWS have in initiating movements stems from reduced excitability in motor regions of the brain. These differences in cortical excitability are also particularly interesting in light of an inverse relationship between fractional anisotropy and motor threshold in AWDS (Klöppel et al., 2008). Finally, despite making an extensive search of the literature, I am aware of no studies in the past twenty years (or beyond) that have applied TMS of any form to CWS. Whether or not CWS exhibit reductions in cortical excitability or elevations of motor threshold relative to CWDS remains to be seen. Establishing such a link could theoretically provide insight into the pathological basis of stuttering.

4.3.7 Miscellaneous studies

There have been a number of intriguing studies that have focused on various aspects of stuttering. Both real and imagined stuttering are associated with increased activation in the SMA, the bilateral insula and cerebellum and decreased activations in

the right auditory cortex (Ingham et al., 2000). Interestingly, the lateral premotor cortex was significantly more active during real rather than during imagined stuttering. DeNil et al. (2008) attempted to examine the neural correlates of simulated stuttering. They compared neural activity when participants were listening to auditorily presented words, pretending to stutter the word, or repeating the word aloud. AWS exhibited stronger activation of the bilateral inferior frontal gyrus, superior temporal gyrus left insula and supramarginal gyrus when stuttering than they did when simply repeating the stimulus word once. Notably however, when stuttering, AWS exhibited higher activation in the right inferior frontal gyrus than did AWDS. These findings were taken to suggest that AWS rely more on the neural systems involved in motor control. They also highlight that increased activation of the superior temporal gyrus is not necessarily associated with an increase in fluency. In a similar study, Wymbs et al. (2013) wanted to assess the inter-individual variation in neural activity associated with stuttering. For some participants, there was overactivation the bilateral superior temporal gyrus, insula and motor regions. While there was not a great deal of overlap in brain activation associated with stuttered speech across participants, there were some important differences in the manner in which stuttering was elicited. In the DeNil et al. (2008) study, subjects pretended to stutter on words, whereas in the Wymbs et al. (2013) study they were more inclined to actually stutter as the words were either likely or unlikely to be stuttered by the individual. Surprisingly, Wymbs et al. (2013) found there was little consistency in brain activation during stuttered speech between subjects and stressed the need to take into account individual differences when examining neural activity associate with stuttered speech. Because the authors did not subdivide stuttered speech into

different types of dysfluencies, it is possible that the individual differences they observed could be attributed to specific types of dysfluencies. This idea receives some support from Jiang et al. (2012) who used pattern analysis to classify stuttering symptoms (elicited by a sentence completion task) as least typical or most typical based on patterns of neural activity. The left inferior frontal gyrus and the bilateral precuneus showed higher brain activity for the most typical but not the least typical symptoms, whilst activity in the left putamen and right cerebellum showed the strongest relationship to the least typical symptoms.

Six studies have examined resting state brain activity in AWS and CWS. This was done with the rationale that task related activity is likely influenced by resting state activity. That is, brain activation during speech tasks may not be unique to speech per se, but rather may be evident in the absence of speech. Ingham et al. (1996) compared cerebral blood flow during rest between AWS and AWDS but found no evidence to support the idea that stuttering was associated with brain abnormalities (see also Braun et al., 1997). In contrast to these studies, Wu et al. (1997) found that AWS have significantly higher uptake of dopamine in the caudate and auditory areas during rest than do AWDS, a result that highlighted the importance of dopamine in the aetiology of stuttering.

Ingham et al. (2012) compared neural activity using PET during eyes closed resting state, oral reading and monologue speech conditions. Here there was significantly increased activation in several regions in AWS during eyes closed rest as compared to the AWDS (e.g. left putamen, left post central gyrus, left preSMA). A number of these regions were also found to be more active during speech (oral read-

ing and monologues, e.g. left superior temporal gyrus, cuneus, right post central gyrus). The observation of similar neural group differences in the absence of an explicit (active or passive) task is intriguing. It implies differences in neural activation between AWS and AWDS previously attributed to task related activity may instead partially be the result of pre-existing differences.

The idea that AWS and AWDS differ in neural activity in the absence of an explicit task is also supported by results from Xuan et al. (2012). These authors who found that AWS have higher amplitude low frequency fluctuations (a measure of local connectivity) during rest than AWDS in several cortical regions associated with speech. These include: the left superior temporal gyrus, middle temporal gyrus, triangular portion of the left inferior frontal gyrus, and reduced amplitude low frequency fluctuations in the bilateral SMA. Abnormalities in resting state connectivity can also be observed using EEG. Joos et al. (2014) found reduced connectivity in the beta band relative to in AWS in the 12.5-18Hz range between left pars triangularis (BA45) and right primary motor cortex (BA4), as well as between the left pars opercularis (BA44) and the right premotor cortex (BA6) and primary motor cortex (BA4) relative to AWDS. The results of Joos et al. (2014) are broadly consistent with the studies above in that they demonstrate abnormal functional activations in speech motor regions even when the subjects (AWS) are at rest.

I am only aware of one study that has investigated functional resting state connectivity in CWS (Chang and Zhu, 2013). These authors focused specifically on the basal ganglia thalamo-cortical loop and found various differences between CWS and CWDS. Specifically, CWS were shown to have reduced functional connectiv-

ity between the putamen and left SMA, superior temporal gyrus, insula/rolandic operculum and stronger connectivity with the right superior frontal gyrus and the putamen. AWS also had reduced functional connectivity between the left SMA and the left putamen, cerebellum and right superior temporal gyrus and increased connectivity between the SMA and the left cerebellum and right paracentral lobule. The authors suggest that differences in these networks likely relate to differences in self-timed movements. This idea is generally consistent with findings of studies showing AWS had weaker connectivity from the left posterior middle temporal gyrus to the putamen and stronger connectivity from the putamen form the thalamus and from the thalamus to the temporal and preSMA (Lu et al., 2010b). AWDS did not show any greater functional connectivity from the left inferior frontal gyrus as compared to AWS. This perhaps suggests that stuttering is not associated with connectivity deficits to the left inferior frontal gyrus.

The only functional neuroimaging study of CWS has been conducted using a resting state paradigm. To the best of our knowledge, no study has used fMRI to examine speech in CWS (though see Sowman et al., 2014, for an MEG study on speech in CWS). There appear to be paradigms that are able to detect functional activation during a speech production task in a very short period of time. Loucks et al. (2011) tested whether it was possible to gather patterns of activity typically associated with overt and covert speech production in an experiment lasting only three minutes. The task required participants to name pictures or silently monitor (view) phonemes. Both AWS and AWDS showed activation in areas classically associated with speech production. Group comparisons revealed that during picture naming, AWS exhibited significantly higher activation in the left motor cortex, the

right precentral gyrus, the right inferior frontal gyrus and insula, bilateral superior temporal sulcus and middle temporal gyrus and the subthalamic nucleus relative to AWDS. This task was successful in identifying the neural correlates of stuttering in an overt task in a limited period of time. To the best of our knowledge, this task has (unfortunately) not yet been applied to CWS.

One study (Sato et al., 2011) used NIRS to measure neural responses to phonemic and prosodic contrasts in AWS, school aged CWS and preschool aged CWS. They found that whereas the AWDS and the CWDS showed a left sided-dominance for phonemic contrasts and a right sided dominance for phonetic contrasts, the same pattern was not observed in AWS or CWS, who both failed to show lateralized responses. Thus it appears that at least some abnormal lateralization is present close to the onset of stuttering. It also demonstrates the viability and utility of less traditional neuroimaging methods in the investigation of the neural correlates of stuttering. Another interesting method that has been used to assess the haemodynamic responses in AWS is diffusion correlation spectroscopy (Tellis et al., 2011). This is qualitatively different from NIRS in that it relies on the motion of the 'scatterers' rather than optical absorption. These authors found an increased cortical blood blow in the left frontal lobe for the AWDS as compared to the AWS and an increase in the right hemisphere CBF in the AWS as compared to the AWDS.

Two studies have attempted to determine what differentiates recovered and persistent stutterers from fluent controls. Kell et al. (2009) noted that functional activation of the left inferior frontal cortex (BA47) was involved in unassisted recovery from stuttering. Those who recover also tend to have fewer structural abnormalities

in this region (two other studies have focused on differentiating persistent and recovered CWS based on structural data. See Chang et al. 2011; Choo et al. 2012 below for more details). Usler and Weber-Fox (2015) examined whether brain responses to semantic and syntactic violations could differentiate between children who persisted and who recovered from stuttering. Relative to canonical sentences (e.g. Pingu is building a castle on the floor.), semantic violations (e.g. Pingu is building a music on the floor.) elicited a N400 effect across groups. Additionally, when compared to canonical phrase structures (e.g. 'Mommy and Daddy look at their son'), semantic violations (e.g. 'Mommy and Daddy look at that their son') elicited a N600 component that was equal in latency and amplitude across the three groups of children (children who had recovered from stuttering, CWS and CWDS). However, when listening to Jabberwocky sentences, the same phrase structure violations elicited a P600 in CWDS and recovered CWS but an N400 effect in persistent CWS. While there were some discrepancies with respect to their earlier studies (e.g. Weber-Fox et al., 2008; Weber-Fox and Hampton, 2008; Weber-Fox et al., 2013), they are likely the result of testing CWS and AWS of different ages or using different baselines when analysing evoked responses. These results suggested that persistent CWS lacked semantic cues required to properly comprehend sentences. Although not specifically focusing on stuttering, Kotz and Schmidt-Kassow (2015) recently showed that patients with lesions in the basal ganglia failed to show a P600 to violations of metric expectancy as compared to healthy controls who showed a P600 to both syntactic and metric violations. Damage to the basal ganglia impairs the amplitude of the P600, given the association of the P600 with the basal ganglia and the basal ganglia with stuttering (Alm, 2004; Chang and Zhu, 2013; Etchell et al., 2014b), it would be

interesting to see if the same component could differentiate between persistent and children who had recovered from stuttering.

4.4 Summary and Conclusion

There are widespread differences of stuttering in white matter integrity in regions involved auditory and motor processing, as well as in tracts connecting areas that support speech production. These same regions also exhibit functional activation abnormalities between AWS and AWDS. A significant portion of the abnormal patterns of activity can be normalised through fluency inducing conditions or treatment. M/EEG studies indicate abnormal patterns of cerebral activation on a very short timescales, many of which are indicative of atypically delayed or increased error monitoring, or decreased motor readiness in AWS as compared to AWDS. Neurostimulation studies in stuttering are limited, but seem to suggest that AWS have reduced cortical excitability in both hand and mouth representations of the motor cortex. There is also some evidence that differences in neural activation during speech (and other tasks) may partially be explained by activations during rest. Various types of dysfluencies are associated with distinct patterns of neural activity but these are somewhat inconsistent across individuals.

Perhaps just as important as what the last twenty years of neuroimaging research in stuttering has shown is what it has overlooked. fMRI scans is the most dominant methodology for acquiring functional brain data - largely for good reason. However, much less is known about the temporal dynamics of the neural underpinnings of speech in AWS. MEG studies of stuttering are very rare in comparison to

the number of fMRI studies. EEG studies have generally focused on psycholinguistic properties rather than speech production. Very few studies have considered the role of neural oscillations in stuttering. Notably, repetitive TMS has only been applied in a single study of stuttering. Theoretically, TMS/TES could be used to disrupt cortical regions and induce stuttering. In doing so, it would establish a direct causal link between cortical regions and stuttering. Furthermore, the vast majority of studies have focused on AWS rather than CWS. Those that have focused on CWS tend to examine structural rather than functional data likely due to the methodological difficulties associated with testing young children. This is despite the fact that there are methodologies and paradigms to gather brain activity from young children in a very short period of time. Overall, while we have learnt much about the brain basis of developmental stuttering, there is still a long way to go.

Chapter 5

The Need to Study Children Who Stutter

There have been a large number of studies on developmental stuttering over the last twenty years.

5.1 Introduction

Researchers have used the various neuroimaging and neurophysiological techniques to investigate the structure and function of the developing brain for over 20 years (Casey et al., 1995). As can be seen from the above research, a growing number of studies have provided important insights into the trajectories of normal brain development (for review see Casey et al., 2005). However, children - and particularly those with developmental disorders - are still under represented in the neuroimaging literature. One possible reason for this is because of the long held perception that it is too difficult to image the brains of children. There have already been a number of reviews discussing the practical, methodological and analytical issues associated with the use of MRI (Gaillard et al., 2001; Peterson, 2003; Poldrack et al., 2002) and M/EEG (Pang, 2011; Trainor, 2012) in children. Nevertheless, in spite of such work, many investigators still have reservations about collecting neuroimaging data from children. Perhaps this is because their concerns have not been readily addressed in previous work or specifically associated with stuttering. These concerns are associated with the appropriateness of the methodology, the effects of participant movement and how to hold a child's attention for the requisite duration of the experiment. They will be discussed in turn.

5.1.1 Methodological problems

Many neuroimaging tools seem inappropriate to use with children. For example, MRI is confining and particularly noisy, which may frighten younger individuals (Byars et al., 2002). The majority of MR head coils are designed to fit adults.

Because children's heads are typically somewhat smaller than adults, there can be slight differences of the positioning of their head in the magnetic field. In turn, these differences can create a poor signal to noise ratios (Gaillard et al., 2001) or large variations in head position may result in substantial alterations in the haemodynamic responses. The fixed sensor geometry of MEG presents a similar problem: Sensors are quite far away from the child's head (Johnson et al., 2010). This is problematic because the strength of the neurally-generated magnetic fields it measures decay exponentially with distance. The increased distance from the sensors to the head will result will be a poor signal to noise ratio (Pang, 2011). Some groups have attempted to overcome this by positioning the head of children so that the region of interest is close to the sensors (Gaetz et al., 2008), though it is not ideal, particularly given the fact that children move (see below). EEG can be time consuming to set up as it requires a substantial amount of time to insert gel into the cap and place the electrodes. TMS and TES both induce physiological sensations like tingling and itching that could be uncomfortable for children. Indeed Davis (2014) offers caution on the use of such methods in young children because there have been very few long terms studies on the effects of brain stimulation on the developing brain. Many researchers are therefore hesitant to utilise this tool in young populations.

5.1.2 Movement problems

Many (though not all) neuroimaging tools (e.g. MRI/fMRI and MEG) are not tolerant of head movement. Friston et al. (1996) has suggested that in some cases, over 90% of the fMRI signal can be attributable to movement. Typical movement

thresholds for fMRI and MEG experiments are between 1-5 mm respectively. Children can have considerable difficulty remaining still for the extended periods of time often required for long experiments. A comparison of head movement between adults and children during experiments suggests that the latter group moves significantly more than the former (Thomas et al., 1999; Yuan et al., 2009). There is even some suggestion that children with developmental disorders move more than typically developing children (Poldrack et al., 2002). Excess movement can distort structural images and render functional data unreliable. Similar issues exist in the case of MEG, if a child's head moves substantially with respect to the sensors in the dewar, the experiment must be abandoned as the data becomes unreliable. This can make it difficult to gather fine-grained temporal or spatial resolution neural data from children. Although EEG is more immune to movement related artefacts, it is also the case that the electrical fields generated by muscular movements is an order of magnitude larger than those associated with the generation of brain activity. This can introduce substantial noise into the EEG recording (Trainor, 2012). In the case of TMS, movement can change the site of stimulation, or drastically reduce the size of motor evoked potentials.

5.1.3 Attentional problems

Regardless of the method used to study the brain, many children are unable to maintain the attention required to enable a sufficient number of trials to be collected. Younger children in particular may not even be able to perform a behavioural task. This not only limits the types of task that can be conducted, but also the amount of

time required to perform them. In the case of MEG/EEG for example, the number of trials is determined by the size of the waveform peak of interest. The rule of thumb in some labs is 30-60 trials for a large peak like the P3, 150-200 trials for medium peaks like the N2 and 400-800 trials when looking at a peak like the P1 (Luck, 2005). It is recommended that this number be doubled when studying young children. The addition of so many extra trials adds substantial time to the experimental protocol. From this perspective, it is clear to see that a 4-year old child would likely have difficulty maintaining attention for over an hour during, for example, a stop signal task which would typically require over 1000 trials and around an hour of recording time. Finally, it is important to point out that attention (or lack thereof) can have an impact on the haemodynamic, evoked or oscillatory response (see for example Arnal and Giraud, 2012). These are of course all valid concerns and are important to consider so as to avoid wasting a significant amount of resources, but it is important to ask whether or not these concerns are truly justified.

5.1.4 Methodological solutions

While it is important to recognise the pitfalls of conducting neuroimaging studies with children, it is also important to question the extent to which beliefs about the associated difficulties are true. There are numerous ways to mitigate the problems associated with the different neuroimaging methods. Recent advances are increasing the opportunities to examine the brains of children even at a very young age. EEG and NIRS systems, with fewer channels or that do not require gel or a large amount of set up time, have provided valuable temporal and spatial data on young CWS (e.g.

Sato et al., 2011). When deciding to use MRI/MEG, researchers can employ training protocols in which a child practises the experimental protocol in a mock/simulated machine before performing the actual experiment. This allows children to become familiar with the novel environment and can substantially reduce anxiety about what will happen in the actual experiment. Rosenberg et al. (1997) reported that children who underwent simulation had lower levels of anxiety and heart rate at the beginning of the scan as compared to those who did not. At the same time however, other groups have (subjectively) reported that there is no difference in the failure rates of scanning sessions when employing such procedures (e.g. Byars et al., 2002). Apprehension about the experiment can be further reduced by making the lab more child friendly. For example, some set up dr so that the laboratory environment resembles a space ship (MEG scanner at Macquarie University, Sydney Australia) or a pirate ship (a CT scanner at New York-Presbyterian Morgan Stanley Children's Hospital, United States). Additionally, where appropriate, it is helpful if a researcher is able to sit with the child to reassure them during the experiment. This can, in our experience, mean the difference between finishing a scanning session and having to abandon it, and is a method that has been employed by others (e.g. Chang et al., 2015).

Slightly lower resolution MRI machines (1.5T) afford the opportunity to scan children within a shorter amount of time at the expense of a reduced amount of spatial resolution (e.g. Beal et al., 2013, 2015). Notably however it is possible to attain structural data from children between 3 and 10 years of age from more conventional 3T scanners (Chang and Zhu, 2013; Chang et al., 2015). While most scanners are optimized for the headshape and size of adults, some institutions are beginning to use

MR head coils that are specifically designed for children and/or infants (e.g. Erberich et al., 2003). This ultimately enhances the signal to noise ratio in the MR signal. In a similar vein, other groups are beginning to utilise paediatric MEG which is custom built so that sensors are close to the brains of children (e.g. Sowman et al., 2014). It is important to point out that the addition of a second MEG system does not necessarily require separate space and may in fact be included in the same magnetically shielded room as the adult system (see Chapter 8). While providing valuable information, the drawback is that building such systems requires significant financial investment. In spite of concerns about neurostimulation with children, recent work has shown that it is relatively safe to use and well tolerated by children aged 5-12 years old (e.g. Andrade et al., 2014). Interestingly, these methods have also shown promise for increasing the efficacy of cognitive training (see for review Krause and Kadosh, 2013).

5.1.5 Movement solutions

Where a structural scan is required for medical purposes (rather than for research), a child can be sedated. Sedation is not generally an option if the researcher is seeking to investigate functional activity of any kind (though for an exception see Souweidane et al., 1999). The effect of movement on neuroimaging (MEG and fMRI) can be mitigated largely by using methods that are more tolerant of movement (i.e. EEG and NIRS). Importantly, each provides either good temporal or spatial resolution respectively. Despite this, actions can be taken to reduce or minimise the effect of movement in other circumstances (i.e. during MRI/MEG). For instance, some

groups (e.g. Temple et al., 2001) limit the child's head movement by using bite bars or by inserting foam between the head and the dewar. While it can be effective in reducing movement, it also increases discomfort which may lead to the child wanting to abandon the experiment. A more viable alternative is to train the child to remain still (e.g. Slifer et al., 1993). Movement thresholds can be decreased until they are within acceptable thresholds. Other groups minimise the tendency for a child to move by interrupting the experiment or video when movement exceeds a pre-determined threshold. In a similar vein, the development of online movement tracking systems can minimise the effect of extraneous movement by allowing online or offline correction for any movement that might occur (e.g. Stolk et al., 2013). Notably, this latter approach is somewhat different from simply minimising online movement because it theoretically allows the retention of a larger number of trials. In the absence of online methods to reduce movement or simulating the experimental environment, analytical techniques can also improve the quality of data (e.g. Wehner et al., 2008). This bodes well for studying children because it does not require additional equipment and can be easily applied to existing datasets.

5.1.6 Attentional solutions

The effect of attention is minimal on scans that are seeking to examine the structure and anatomical connectivity of the brain (e.g. DTI and VBM). These forms of scans are becoming increasingly common in both typically developing children and in clinical populations (e.g. Chang and Zhu, 2013; Chang et al., 2015). However, there are of course times when researchers desire to investigate differences in the

function of the brain between groups. As detailed above, Loucks et al. (2011) tested the feasibility of collecting functional neuroimaging data from a speech production task in adults within 3 minutes with the intent of applying the methodology to CWS. Notably, while the data quality may not be as good in younger children, it would theoretically be possible to run the paradigm for 3-4 times as long (i.e. 12-15 minutes) and attain a relatively high signal to noise ratio without necessarily being limited by children's ability to sustain attention. In most cases, studies examining brain function in children have done so by using tasks that require minimal attention. Work by Mahajan and McArthur (2011) has shown that while watching a movie with an audible soundtrack can degrade the quality of auditory ERP responses in children, a movie with an inaudible soundtrack (i.e. no sound) does not. Having children watch silent movies is a method that has been employed in a number of subsequent experiments (e.g. see Chapter 10/11 Shahin et al., 2010). More recently, some authors have embedded their experimental protocol into a game (e.g. Cheyne et al., 2014). This keeps young children engaged and allows researchers to acquire data that would not be otherwise possible when using a more traditional framework. Although it has not yet been demonstrated for more complex tasks, the success of the above example shows that this method of investigation is promising. Moreover, while it is very difficult to collect behavioural and neuroimaging data from young children without embedding experimental protocols in a game, it is not beyond the realm of possibility. Sowman et al. (2014) collected neuromagnetic responses from CWS and CWDS aged between 3 and 6 years old during a picture naming task. While the recordings were taken over multiple sessions, it illustrates the feasibility of conducting simple behavioural experiments on young children while they must

perform an overt task. Ideally such tasks should be kept as simple and as short as possible.

The above studies highlight that the ability to image the brains of children is indeed possible. It seems that the factors that often dissuade researchers from conducting experiments with young children can, with sufficient effort, be overcome. But what is meant by the term 'children'? And even if we have the capacity to study children, it is vital to ask why should we study them? More specifically, what information do we get from studying children that we cannot get from studying adults?

5.2 The role of development

Many developmental disorders are thought to be the result of structural and functional abnormalities in the brain that emerge at a very early age. As these changes impact the course of normal brain development, the disorders can only really be understood from a developmental perspective (Karmiloff-Smith, 1998). Of those that have studied children the definition of 'children' can vary widely. For example, Sowman et al. (2014) studied CWS between 3 and 6 years of age; Jansson-Verkasalo et al. (2014) has studied CWS aged between 6 and 9 years and Weber-Fox et al. (2008) studied CWS between 9 and 13 years of age. The brain structures and functions that cause stuttering are very likely to overlap with those that are maturing at the onset of the disorder. Conversely, the brain regions that mature after the onset of the disorder could not logically be involved in the cause of stuttering. Given there are significant differences in the neural response of typically developing 3-4 year old

children and 8-10 year old children to sounds (Shahin et al., 2010), it stands to reason that the brain's response in CWS who are aged 3-6 is also probably very different from the response in CWS who are aged 10-12 or 16-18.

The abnormalities associated with stuttering not only impact brain regions themselves, but also impact the course of normal brain development. Because the brain has a very protracted development (Giedd and Rapoport, 2010), it would not be surprising to find that the effects of stuttering are manifested differently with age. Whereas CWS, exhibit a relationship between the levels of grey matter volume in sensory and motor regions CWDS do not (Chang et al., 2015). These authors showed there was a positive correlation between fractional anisotropy of the white matter in the left inferior frontal gyrus and age in CWDS but not in CWS. Interestingly, there was a tendency for these differences to become greater with age (see also Beal et al., 2015). Thus abnormalities occurring early on in development seem to impact the course of later development. For this reason, when making claims about the cause of developmental disorders, it would be necessary to study children who are as close to the age of onset of the disorder as possible. By studying 'children', researchers are able to gain insight into the abnormal developmental trajectory of the brain in stuttering, something that is unavailable when studying adults or perhaps even older children. When looking at the differences between CWS and CWDS (and other children with developmental disorders), it would be beneficial to study children who are as close to age of onset as possible.

5.3 Neural plasticity

It is well established that the brain changes in response to experience (e.g. Lappe et al., 2008). For example, the hippocampus - the region of the brain that processed spatial memory - of London Taxi cab drivers is larger than the hippocampus of bus drivers (Maguire et al., 2006). Strangely, this phenomenon is rarely taken into consideration when studying neurodevelopmental disorders (see for a discussion Peterson, 2003). This is problematic because neural plasticity can confound the interpretation of results. At best, studying adults provides an incomplete picture of brain responses to stuttering and at worst studying adults can lead to empirically incorrect conclusions. These will be considered in turn: A pertinent example of this is that it is sometimes observed that the right inferior frontal gyrus is overactive in AWS and that its activity is negatively associated with stuttering severity (Braun et al., 1997; Preibisch et al., 2003). This is possibly an adaptive compensation to stuttering. But in order to be absolutely sure of such a conclusion, it would need to be shown that such a change was absent in CWS. Indeed, several studies have now shown that this abnormal activation pattern is not present in CWS (Chang and Zhu, 2013; Beal et al., 2013; Sato et al., 2011).

Of course, the issue is much more complex than what is described here. As such, there is little agreement as to whether right hemisphere overactivations are adaptive or maladaptive (see for discussion Kronfeld-Duenias et al., 2014). An adaptive activation that is effective at ameliorating stuttering would be negatively correlated with stuttering, but an adaptive activation that is not effective at ameliorating stuttering could be positively correlated with it. More generally, the lack

of a significant correlation between neural activity and stuttering needs to be interpreted with caution. Many studies include only relatively small numbers of subjects making it hard to detect significant relationships between variables at the subject level. Furthermore, measures of stuttering severity (commonly used as a correlate with neuroimaging data) vary widely across studies. However, regardless of whether neural activation is adaptive or maladaptive, multiple attempts to recruit right hemisphere structures could lead to morphological changes elsewhere in the brain (e.g. Choo et al., 2012). In line with this reasoning, a number of publications report increases in the anterior corpus callosum in AWS (e.g. Cai et al., 2014b; Civier et al., 2015; Cykowski et al., 2010) which have not been reported in CWS.

Consider another example where the basal ganglia are positively correlated with stuttering severity (e.g. Giraud et al., 2007). This is a frequent finding in AWS (e.g. Lu et al., 2010b; Toyomura et al., 2011). One possibility is that this reflects a cause of stuttering, but it is also possible that this reflects a maladaptive response to stuttering (Kell et al., 2009). The only way to determine which of these is occurring is to study the brains of children: If it is a maladaptive response, one would not expect it to be present as extensively in CWS because their brains have not yet had time to adapt to it. Conversely, if the abnormality is casually related to stuttering, then one would presumably expect such a response to be evident in CWS (as well as AWS). Although this is a reasonable assumption it is also important to acknowledge the very real possibility that compensation may begin as soon as a child begins to stutter. The evidence for this assumption is mixed. For example, whereas Chang and Zhu (2013) reported no increases in right frontal activity in CWS, a later study by the same group, using a larger sample (Chang et al., 2015) reported that CWS

did exhibit increased in fractional anisotropy in right cerebellar regions. Thus it is possible that alterations in neural activity (possibly linked with compensatory activity) may emerge at a very young age. Overall, the study of neurodevelopmental disorders in adults provides an incomplete picture of the relationship between causal and compensatory changes in the brain in stuttering.

Failing to consider the role of neural plasticity can lead to what are potentially incorrect conclusions. Several behavioural studies have found no difference between the accuracy and variability of paced finger tapping between AWS and AWDS (e.g. Max and Yudman, 2003). This could, quite reasonably, lead one to conclude that stuttering is not a disorder of timing (e.g. Max and Yudman, 2003) or perhaps that they do not have a problem in producing isochronous rhythmic movements. This may well be correct, however, such a conclusion may also be premature as AWS could have learnt to compensate for this deficit. As mentioned above, the right inferior frontal gyrus is overactive in AWS and is negatively correlated with stuttering severity (Preibisch et al., 2003). This same structure is also part of a 'core timing network' (Wiener et al., 2011). Let us assume for the sake of argument that it is an effective adaptive compensatory activation. This would (if effective) obscure subtle (or even gross) behavioural differences between groups. This may include behaviour on simple tasks such as those involving finger tapping (see Neef et al., 2011a). So, the absence of differences in behavioural performance between AWS and AWDS, does not necessarily mean that there are no neural differences. It also does not warrant the conclusion that stuttering is unrelated to temporal processing. If stuttering was unrelated to temporal processing, it would be expected that like adults, there are no behavioural differences in CWS and CWDS in accuracy

or variability of tapping, clapping or discrimination of rhythms. On the other hand, if the lack of differences between AWS and AWDS is attributable to neural plasticity, there might be behavioural differences between CWS and CWDS if they have not yet learnt compensatory strategies. As it stands, a number of studies have reported behavioural differences in the perception and production of rhythms (Olander et al., 2010; Falk et al., 2014; Wieland et al., 2015) suggesting that stuttering is indeed a temporal processing disorder. Interestingly, one study has reported differences in the neural response to rhythms and this has found significant differences between CWS and CWDS (see Chapter 11). These examples highlight the fact that neuroimaging data from children complements neuroimaging data from adults.

In summary, researchers seeking to study developmental disorders should if it is possible, study the brains of children. This will complement their studies of adults and provide a more holistic picture of the developmental disorder. Studying the brains of children can be achieved with relative ease depending on the methods that are employed and the context in which the experiment is run. Finally, I stress that the methodological issues described in the later part of this paper are not exclusive to stuttering but rather are applicable to all developmental disorders. Future research should compare longitudinally, the brains of children at risk of stuttering to identify structural and functional biomarkers that differentiate those who continue to stutter to those who recover from it. This will aid in unravelling the mystery of stuttering.

Chapter 6

Multimodal Neuroimaging Evidence for a Brain Timing Deficit in Stuttering

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(see Appendix D for original article)

6.1 Introduction

According to the World Health Organisation (2010, para. F98.5), stuttering is 'speech that is characterised by the frequent repetitions or prolongation of sounds or syllables or words, or by frequent hesitations or pauses that disrupt the rhythmic flow of speech'. Repetitions typically consist of a repetition of part of a word, a whole word or a phrase (e.g. re-re-re-repetitions). Prolongations consist of a lengthening of the sounds within a word (e.g. prrrrrrrolongations). Complete interruption to the flow of speech, known as 'blocking' is also a common symptom of stuttering. Blocks are where there is a length of time where no form of speech is produced either within words (e.g. block-(pause)-ing) or between words. In most cases, stuttering emerges between 2 and 5 years of age, around the time children start preschool. Stuttering has a prevalence of around 5% in early childhood but due to the fact that many children recover spontaneously, the prevalence across the general population is closer to 1% (Yairi and Ambrose, 2013). This percentage of stutterers who do not recover generally experience poorer social, emotional and mental health (Craig et al., 2009; Iverach et al., 2009) and elicit negative reactions from others (Langevin et al., 2010). Stuttering is also associated with secondary or associated signs that include facial grimaces, forced effort and eye-blinks (Conture and Kelly, 1991; Riva-Posse et al., 2008). These secondary signs further impair the ability to communicate effectively and exacerbate the problems that result from the primary symptoms. Importantly, such secondary signs imply that stuttering is not solely confined to the domain of speech but rather a disorder of motor control that manifests primarily in the domain of speech because of the extreme timing and sequencing demands required for that

function. Moreover, while difficult, it is not impossible to detect differences related to stuttering in the manual domain (e.g. Ambrose, 2004; Max and Yudman, 2003).

Packman (2012) argues that the necessary condition for stuttering, i.e. the one thing each person who stutters must possess, is a neural anomaly that weakens the integrity of the speech motor system. In this weakened state, the speech motor system is rendered more susceptible to breakdown when various features of the spoken language place increasing demand on the system (Packman, 2012). The point at which stuttering is triggered is modulated according to individual and environmental factors such as levels of physiological arousal. Here I take the view that the necessary condition for stuttering (which unless otherwise specified is used to refer specifically to developmental stuttering) is the presence of a neural anomaly in timing.

The following account proposes the hypothesis that the core disorder of stuttering is a deficit in brain timing-networks. This article is not an exhaustive review of the literature on stuttering or the arguments surrounding the cause of the disorder, but rather a hypothesis as to one of the possible causes of stuttering. The proposal that timing is important for speech (see Lashley, 1951; Martin, 1972; Strait et al., 2011) and even speech disorders like specific language impairment (Tallal et al., 1995) dyslexia (Goswami, 2011) or indeed stuttering (Alm, 2004) is not new. In the later case, the idea that stuttering relates to a deficit of timing follows from the observation that regular external stimulation temporarily alleviates stuttering (see for a revision, Alm, 2004; Snyder et al., 2009). The novel aspect of this article is that it expands on previous research suggesting that dysfunction within a brain network that supports internal timing [comprised of the basal ganglia and the supplemen-

tary motor area (SMA)] is causing stuttering and that a secondary system which utilises external timing cues to sequence movements [comprised of the cerebellum, the premotor cortex (PMC) and the right inferior frontal gyrus] is compensating for stuttering. Specifically, I propose that an internal timing network (ITN), largely equivalent to the 'medial system' proposed by Goldberg (1985) is involved in internally timed movement (movement performed in the absence of external timing cues) and is causally related to stuttering. I further propose that an external timing network (ETN), largely equivalent to the 'lateral system' proposed by Goldberg (1985), with the addition of the right inferior frontal gyrus, is involved in externally timed movement (movement performed in the presence of external timing cues) and provides a substrate for timing compensation in stuttering. Importantly, I am not suggesting that neural deficits in structures underlying timing is the sole cause of stuttering, but rather one of many possible deficits that could lead to stuttering. In this section, I first present multimodal neuroimaging evidence for the possible causal involvement of ITN in stuttering before moving on to discuss putative compensatory roles of the ETN.

There is ongoing debate as to whether some brain regions are specifically dedicated to processing time or whether the capacity to process time is intrinsic to each region of the brain directly through the activation of sensory processes (for review see Ivry and Schlerf, 2008). There already exist reviews outlining the cognitive and neural architecture proposed for how individuals represent a sense of time (e.g. Buhusi and Meck, 2005), how different sensory networks interact with core timing networks across different tasks (e.g. Merchant et al., 2013) as well as evidence for common timing mechanisms across manual and oral movements (e.g. Franz et al.,

1992). While the questions of how and where time is processed in the brain are of considerable practical and theoretical interest, such a discussion is outside the scope of this article. Here I argue that the ETN is primarily active when an individual is timing their movement to an external rhythm and that it is particularly active during early exposure to rhythm or when the rhythm is difficult and is not easily internalized. In contrast to this, the ITN is primarily active when an individual is making rhythmic motor movements that are not specifically timed to an external stimulus. Importantly, the two systems can be active simultaneously such as when an individual is pacing their movements to an external stimulus and is internalizing that rhythm. Practically, this means that results of functional magnetic resonance imaging (fMRI) studies may show no difference in brain activation between conditions that supposedly bias internally or externally-timed movements; however, disruption of these systems via inhibitory transcranial magnetic stimulation (TMS) should yield selective interference in behavioural performance. What follows is a brief overview of studies supporting a dissociation between the ITN and the ETN in timing tasks.

There is strong support for the involvement of the ITN during timing tasks from a number of fMRI, magnetoencephalography (MEG), lesion and TMS studies. For example, a recent fMRI study has found that the basal ganglia and the SMA tend to be active when movements are internally as opposed to being externally timed (Coull et al., 2013). Similarly, it has been shown using finger tapping tasks, that the basal ganglia and the SMA are active during the continuation phase (no external pacing stimulus, hence an internally-timed process) but not the synchronisation phase (with external pacing, hence externally-timed) of the task (Rao et al., 1997). In particular, the basal ganglia are more active during the performance or

tracking of simple rhythms, i.e. those that are easier to internalize, compared to complex rhythms (Grahn and Rowe, 2009, 2013; Geiser et al., 2012). The fact that fMRI studies show an overlap of neural activity during synchronisation and continuation tapping (e.g. Jäncke et al., 2000; Jantzen et al., 2004) provides little support for a functional distinction between brain networks supporting internal and external timing; however, evidence from lesion and TMS does support such a dissociation between the INT and the ETN and their respective functions. Studies show that individuals with bilateral lesions to the basal ganglia perform poorly on the continuation phase of the finger-tapping task (Coslett et al., 2010) and are also poor at adjusting to accelerations and decelerations in tempo (Schwartze et al., 2011). Disruption of the SMA by inhibitory TMS impairs accuracy of continuation tapping whilst leaving the accuracy of synchronisation tapping intact (Halsband et al., 1993).

There is also evidence for the involvement of cerebellum and the PMC in the ETN. Inhibitory TMS of the cerebellum has been shown to disrupt synchronisation to auditory (Del Olmo et al., 2007) and visual pacing (Koch et al., 2007; Théoret et al., 2001). This disruption appears to be selective because lesions to the cerebellum do not affect performance during the continuation phase of the finger-tapping task (Spencer et al., 2003). Likewise, a number of studies show that inhibitory TMS of the left PMC disrupts the synchronisation tapping (Bijsterbosch et al., 2011; Pollok et al., 2008) and that this effect is specific to external pacing, as no effect of TMS is observed on continuation tapping (Del Olmo et al., 2007) or when tapping in the presence of, but not in time with, a scrambled beat (Kornysheva and Schubotz, 2011). Taken together, there indeed appears to be a functional dissociation of the ITN and the ETN in healthy adults. I now turn to neuroimaging studies to demonstrate how

these systems are impaired in people who stutter.

6.2 Neuroimaging Studies of the Internal Timing Network in PWS

A number of neuroimaging studies implicate the basal ganglia or components thereof in the etiology of stuttering. For example, when comparing the fluent and dysfluent speech of people who stutter (PWS) to people who do not stutter (PWDS), Wu et al. (1995) found that PWS exhibited less activity in the caudate during both dysfluent speech and fluent speech. This lowered activity was suggested to be a trait marker for stuttering. The basal ganglia has also been related to the most typical symptoms of stuttering at an individual level (Jiang et al., 2012). These authors elicited stuttering during a sentence completion task and classified repetitions, pauses and prolongations as being either least typical or most typical of stuttering based on patterns of haemodynamic responses. Jiang et al. (2012) found that one of the activation patterns contributing to this separation of most and least typical symptoms was a reduction in basal ganglia activation. Although the aforementioned studies provide a correlative link between the putative ITN and stuttering, they do not unambiguously support the notion that the ITN causes stuttering. Because those studies were conducted mainly in adults, and stuttering is a disorder that appears in childhood, it can therefore be hard to determine whether anomalous basal ganglia activations observed in PWS are related to the cause of stuttering or are compensations for it.

In contrast, structural and functional abnormalities in children who stutter

(CWS) are likely to be more indicative of the causative agents in stuttering because children have not had as much time to adapt to stuttering as adults. Chang and Zhu (2013), examined functional connectivity in CWS and children who do not stutter (CWDS) aged 3-9 and found reduced levels of connectivity between the putamen and the SMA, superior temporal gyrus and cerebellum and similarly between the SMA and the putamen, superior temporal gyrus and cerebellum. Chang and Zhu (2013) concluded that CWS exhibited reduced activity in areas responsible for self-paced movement as compared to CWDS. Similarly, a recent voxel based morphometry (VBM) study conducted in CWS, found less grey matter volume in the bilateral inferior frontal gyri and the left putamen but more grey matter volume in the right rolandic operculum and the right superior temporal gyrus relative to CWDS (Beal et al., 2013). In another study, Foundas et al. (2013) measured the volume of the caudate in right-handed boys who stutter and compared them to right-handed boys who did not stutter. They found that male CWS exhibited significantly less volume in the right caudate as compared to male CWDS. These studies suggest that even at a very young age, CWS exhibit abnormalities in structure and connectivity in the ITN. A recent MEG study examined lateralization of brain functions in preschool CWS and CWDS during a picture-naming task (Sowman et al., 2014). These authors found that speech was strongly left lateralized in both groups. Although not explicitly focusing on the ITN, this study demonstrates that much of the abnormal activation observed in the cortical right hemisphere in adults is the result of years of compensation for stuttering rather than being causally related to it. Moreover, that there were no differences between CWS and CWDS in cortical activations further hints at the possibility that stuttering is caused by deficiencies in subcortical

regions. Overall, these studies provide strong support for viewing stuttering as a disorder of the BG. Since the basal ganglia seems responsible for internal timing of movement, they provide indirect support that stuttering is a disorder of internally timed movement.

To implicate the ITN in stuttering, structural or functional abnormalities should be evident in these structures in both children and adults who stutter and the neural deficit necessary to cause stuttering should be present irrespective of whether or not a subject is performing a task. Ingham et al. (2012) examined speech during oral reading and monologues as well as during a rest condition and found that PWS were different to PWDS in both the medial (ITN) and lateral (ETN) systems proposed by Alm (2004). PWS had significantly more activity in the basal ganglia (including the left putamen) during an eyes closed rest condition but significantly less activity during speaking conditions. This was thought to result in difficulties in performing fine-grained movement that may extend to speech and explain the fact that other studies observed increased activation of these regions in speech conditions like oral reading and monologue. More specifically though, if it is the case that the basal ganglia are overactive during rest and not just underactive during speech, it would indicate abnormalities in stuttering are not solely confined to speech. That is to say, the problem spans a number of domains because there are functional differences in neural activation occurring in the absence of speech. If abnormalities of the ITN are causally related to stuttering, then it could be expected that effective speech therapy should produce measurable changes in the neural activity of these structures rather than in the areas compensating for stuttering. To this end, Giraud et al. (2008) examined neural activity using fMRI before and after speech therapy in a

group of PWS. Therapy consisted of three weeks of undergoing an inpatient program focusing on biofeedback for syllable prolongation, soft voice onset and smooth sound transition. The researchers found that activity in the caudate positively correlated with stuttering severity before speech therapy but not after. Since the caudate was positively correlated with severity rather than negatively correlated with it, the speech therapy appeared to target causal rather than compensatory regions.

Similarly, if the ITN is related to stuttering this will not only be reflected in measures of neural activity but also in terms of the connections within the ITN. Lu et al. (2010b) used structural equation modelling to compare causal relationships and function in the ITN in PWS and PWDS during a picture-naming task. Although there were no significant differences between stuttering and non-stuttering speakers in the output of the SMA to the BG, there were significant differences between the groups in the output of the basal ganglia to the SMA. More specifically, whereas PWDS showed a strong negative projection from the basal ganglia to the pre-SMA, PWS showed a positive projection from the basal ganglia to the pre-SMA Lu et al. (2010b) interpreted their finding of abnormal output of the basal ganglia to the SMA as reflecting the difficulties PWS have in updating the timing and sequencing of movement. Interestingly, like Lu et al. (2010b), a number of other studies have also shown altered patterns of activity in the SMA in relation to the perception and planning of speech in stuttering (Chang et al., 2009, 2011). Taken together, these findings, are consistent with the notion that stuttering is the result of dysfunctional processes that engage core structures within the proposed ITN: the basal ganglia and the SMA.

6.3 Lesion Studies of the ITN in PWS

If dysfunction in the ITN is thought to cause stuttering, then it follows that damage to these regions may result in stuttering. When stuttering develops following a lesion to the brain it is known as acquired or neurogenic stuttering (for review see Lundgren et al., 2010). There is evidence that damage to the ITN results in stuttering. For example a recent study by Tani and Sakai (2011) examining five patients with basal ganglia lesions (two with bilateral putamen lesions, two patients with bilateral basal ganglia lesions and one patient with a left putamenal lesion) but without aphasia, found that they exhibited dysfluencies such as syllable repetitions, part word repetitions and frequent blocks. Importantly, these patients' symptoms mimicked the characteristics of developmental stuttering in that almost all stuttering occurred on the initial syllable of a word. In a number of case studies, Ciabarra et al. (2000) describe a right-handed woman with a left basal ganglia lesion, and a woman with a left corona radiata, putamenal and subinsular infarct who both stuttered. Similarly, a number of different case studies have reported the onset of stuttering following damage to the SMA (Ackermann et al., 1996; Alexander et al., 1987; Chung et al., 2004). Furthermore, direct electrical stimulation of the SMA has also been shown to induce stuttering (Penfield and Welch, 1951). These findings are consistent with the notion that damage to the SMA can cause speech disorders and that the SMA is linked with the rhythmic control of speech (Jonas, 1981). This and other works have prompted investigation into the role of the SMA in rhythmic movements of the mouth (MacNeilage and Davis, 2001) as well as dissociations between the pre-SMA and the SMA-proper in rhythmic timing (Schwartze et al., 2012).

6.4 Neuroimaging studies of the ETN in PWS

There are studies hinting that deficits to the ITN are causing stuttering, but what proof is there that the ETN is recruited to compensate for this? To answer this question, I turn to fMRI studies of PWS. Braun et al. (1997) found the cerebellum to be overactive in PWS during stuttered and fluent speech and it has been suggested that this is a compensatory mechanism for stuttering (see also Alm, 2004). In a meta-analysis of PWS, Brown et al. (2005) identified three neural signatures of stuttering. These neural signatures were the absence of auditory activation bilaterally, the over-activation of the right inferior frontal gyrus and the over-activation of the cerebellum. These findings have since been partially replicated by Lu et al. (2010b) who found over-activation of the right inferior frontal gyrus and the cerebellum (but not the absence of bilateral auditory activation) and interpreted them as compensating for stuttering. Ingham et al. (2012) examined speech during oral reading and monologues as well as rest, finding that PWS exhibited increased cerebellar activity which was negatively associated with stuttering, indicating that the ETN may indeed be compensating for the ITN. A similar study, examined resting state functional connectivity of PWS before and after speech therapy in stuttering and non-stuttering adults (Lu et al., 2012). These authors found increased resting-state-functional-connectivity between the midline cerebellum and a network of regions (comprised of the medial frontal gyrus, the SMA and the left inferior frontal gyrus) at rest for PWS relative to PWDS. For the PWS who received intervention as compared to the PWS who did not receive intervention (and PWDS), the resting-state-functional-connectivity in the midline cerebellum returned to normal levels and was correlated

with an increase in fluency. As such, Lu et al. (2012) suggested the cerebellum was likely compensating in stuttering. In addition to these, other studies have associated the cerebellum with compensatory activation in PWS (e.g. Watkins et al. (2008); DeNil et al. (2008)).

While there is overlap in the neural structures responsible for external timing and compensation for stuttering, it does not automatically follow that the ETN is compensating for deficits in internal timing in PWS. However, there is fMRI evidence showing that the cerebellum and the right inferior frontal gyrus specifically compensate for deficits in the basal ganglia with respect to timing tasks in those who have Parkinson's Disease. For example, Jahanshahi et al. (2010), investigated the differences in neural activation between Parkinson's Disease patients and controls in and the synchronisation continuation task. They also examined the effect of administering apomorphine (a non-selective dopamine agonist) on neural activation in the Parkinson's Disease patients. Results showed that for healthy controls synchronisation and continuation tapping (relative to a control reaction time task) was associated with significantly greater activation in the nucleus accumbens and caudate, a pattern not found in Parkinson's Disease patients. In contrast, individuals with Parkinson's Disease showed greater activation in the bilateral cerebellar hemispheres, right thalamus and left midbrain during both phases of finger tapping. Administration of apomorphine to the Parkinson's Disease patients appeared to normalise activity, both increasing the connectivity between the caudate and putamen and frontal regions as well as decreasing activity in the cerebellum. Thus, the authors suggested that increased cerebellar activation was likely compensating for the impaired functioning of the BG. Sen et al. (2010) found increased cerebellar-thalamo-

cortical activation as Parkinson's Disease progressed, perhaps indicating an increasing need to compensate for loss of function in the striato-thalamo-cortical networks. This increase was only observed during continuation tapping and was not evident during synchronisation tapping suggesting that the cerebellar-thalamo-cortical (i.e. the ETN) was compensating for the cerebellar-thalamo-cortical (i.e. the ITN). The dissociation between the ITN and the ETN may seem problematic given both the cerebellum (part of the ETN) and the SMA (part of the ITN) are thought to compensate for deficits in the basal ganglia during self initiated hand movements in the early stages of Parkinson's Disease (Eckert et al., 2006). Nevertheless, this could suggest that part of the ITN (the SMA) may still be able to compensate for deficits in other parts of the ITN (the BG) when degeneration is not particularly severe.

6.5 Compensation by the Right Inferior Frontal Gyrus in Stuttering

An increasing number of studies have reported anomalous activation of the right inferior frontal gyrus in a variety of speech tasks (e.g. Brown et al., 2005; Fox et al., 1996; Sowman et al., 2012) in PWS. Several studies found that increases in right inferior frontal gyrus activation during overt reading (Lu et al., 2010b; Preibisch et al., 2003) that were positively correlated with speech fluency in PWS and thought to be a nonspecific compensatory mechanism because the activation was not specifically related to speech production. Examining the effect of external auditory pacing on the speech of PWS Toyomura et al. (2011) found that, relative to a PWDS, the

PWS showed more activation in the right inferior frontal gyrus (along with bilateral auditory cortices) during both choral speaking and when speaking in time with an isochronous metronome. There are also reports of increased right frontal connections in adults who began stuttering as children (i.e. developmental stuttering) relative to adults who began stuttering later in life following a psychological trigger and without evidence of brain injury (Chang et al., 2010). This evidence suggests that the longer a PWS has been compensating for their stuttering, the greater the activity in the right inferior frontal gyrus.

It is worth noting that Goldberg's formulation of the lateral system (upon which the ETN partially maps) does not contain the right inferior frontal gyrus. Why then should right inferior frontal gyrus be considered a part of an ETN that compensates for a dysfunctional ITN in stuttering? This question is particularly relevant when considering that the simplest explanation for right inferior frontal gyrus involvement in stuttering is that it compensates for deficits in the left inferior frontal gyrus (see Kell et al., 2009). Kell et al. (2009) associate the left inferior frontal gyrus with processing of rhythm and sensorimotor feedback and it is possible that the right inferior frontal gyrus may perform a similar function. Recently, the right inferior frontal gyrus has been recognised as part of a 'core timing network' (Wiener et al., 2010) that is recognised to be strongly connected both functionally and structurally to the ITN (Kung et al., 2013; Brittain and Brown, 2014). In particular, the right inferior frontal gyrus may only become active when a task is more demanding. That is to say, the difficulty of compensating for deficits in internal timing by external timing regions might account for why there was over-activation of only the cerebellum during speech, but not the right inferior frontal gyrus during rest

in PWS (Lu et al., 2012). A second, though not mutually exclusive explanation is that while the cerebellum is able to compensate for timing deficits, its ability to do so is limited. This is evident in the case of individuals with Parkinson's Disease where behavioural performance worsened despite increases in compensatory activation in the cerebellum (Sen et al., 2010). A similarly limited ability of the cerebellar systems to compensate for deficits in timing may be occurring in PWS as evidenced by the reduced integrity of cerebellar tracts in both the left and the right hemispheres (Connally et al., 2014). Since the ETN has a limited capacity to compensate for deficits in the ITN, the assistance of the right inferior frontal gyrus may be required to maintain normal timing functions. A third possible explanation is that the model proposed by Goldberg (1985) (where the ETN is comprised of the cerebellum and the PMC) is incomplete and requires the addition of the right inferior frontal gyrus as a secondary part of the system. Importantly, the right inferior frontal gyrus is not likely to be the only region that is be compensating for stuttering. There are many other regions like the orbitofrontal cortex that could found to be compensating depending on the task and motor regions involved (see Kell et al., 2009; Sowman et al., 2012). Our contention is that the right inferior frontal gyrus forms part of a network that compensates for deficient internal timing.

6.6 Behavioural studies of timing in PWS

If stuttering is the result of dysfunction in the ITN, and the ITN is important for timing, then it follows that PWS should exhibit deficits in behavioural performance on timing tasks. To this end several groups have found significant differences in asyn-

chrony and variability of tapping between PWS and PWDS. For example, measuring the timing variability of reading sentences or nursery rhymes or tapping, Cooper and Allen (1977) found that PWS were consistently more variable in the length of time it took them to read sentences, paragraphs or nursery rhymes, and in their inter-tap intervals compared to PWDS. Brown et al. (1990) found that PWS were slower and less variable than PWDS at repeating the phrase 'ah' and tapping their fingers as at their own pace compared to PWDS, findings they interpreted to represent less flexible timing systems which were more susceptible to breakdown. Similarly, when examining the timing intensity and variability of externally timed speech, Boutsen et al. (2000) showed that although both PWS and PWDS exhibited similar intensities when producing syllables, PWS were significantly more variable in their inter-onset vocalization times (analogous to the inter tap interval in tapping tasks). Additionally, Zelaznik et al. (1997) found that PWS were more variable on bimanual finger tapping (something more demanding than unimanual finger tapping) relative to PWDS. Similarly, Hulstijn et al. (1992) found that on a task which required the coordination of finger tapping and vocal responses (tapping in time with vocalising the word 'pip'), PWS exhibited greater variability than PWDS. More recently, Olander et al. (2010) compared hand-clapping variability in CWS and CWDS. While there was no difference in mean clapping rate, there were significant differences between groups in the variability of the clapping rate. This variability was bimodally distributed, with 60% of CWS showing variability that was greater than the worst performing CWDS. The remaining CWS showed variability in clapping that overlapped with that of the CWDS. Interestingly, this number approximately corresponded to the number of children that spontaneously recover and whose stuttering persists. As a result, the

authors suggested that the motor timing deficit may be predictive of recovery from stuttering. Later, Foundas et al. (2013) found that when male CWS were required to tap as fast as possible in a given time period, most were better when tapping with their left rather than right hands as compared to most male CWDS who showed an advantage for their right hand. A recent behavioural study has found robust differences in tapping performance between CWS who stutter compared to CWDS (Falk et al., 2014). In contrast to the CWDS, the CWS not only tapped earlier and were less consistent in tapping, but also failed to improve with age.

However, a number of studies have compared the asynchrony and variability of PWS and PWDS on externally or internally timed vocal or oral motor movements and found similar levels of variance between the groups (e.g. Melvine et al., 1995; Hulstijn et al., 1992). Similar results have been obtained by Zelaznik et al. (1994) who compared PWS and PWDS on externally and internally timed manual responses for isochronous intervals and found that the groups did not differ in behavioural performance. Likewise, Max and Yudman (2003) found PWS and PWDS displayed highly similar levels of asynchrony and variability for finger tapping and producing vocalisations for multiple isochronous intervals. Overall, the behavioural studies investigating the timing abilities of PWS have produced mixed results. While some studies have found differences between PWS and PWDS, many have failed to find differences between groups. From this research, it might seem appropriate to conclude that stuttering is not a disorder of timing and that the links between stuttering and deficits in production of timed limb movements is tenuous at best. One possible explanation is that motor control of limbs and speech is different both centrally and peripherally (Kent, 2000). However if this were indeed the case, then it

would be hard to explain why some studies did find significant differences between PWS and PWDS in non-speech motor tasks. Moreover, there is evidence of common timing systems across modalities (Franz et al., 1992) and it has been stressed that the behavioural differences between PWS and PWDS are not confined to the speech production system and instead appear to be generalised deficits (Max and Yudman, 2003). There are other possible explanations for the failure to find behavioural differences between groups which can, in part, be attributed to compensatory neural activity and task difficulty.

6.7 Tentative suggestions for timing deficits in PWS

The substantial number of studies finding no difference in timing behaviour in PWS and PWDS is inconsistent with the notion that stuttering could be considered a disorder of timing. How then can these seemingly paradoxical findings be resolved with the consistent observation that neural regions involved in internal timing display anomalous function and structure in stuttering? The absence of a difference at a behavioural level does not imply the absence of differences at a neural level. Even a task as simple as tapping a finger or vocalising to a metronome recruits a complex network of brain regions each with a variety of different functions (Repp and Su, 2013). Moreover, there may be differences at the neural level in the absence of differences at the behavioural level precisely because PWS are compensating for deficits in internal timing. Such a possibility is highlighted by the findings of Neef et al. (2011a), who, utilising inhibitory TMS, showed PWS did not exhibit behavioural differences in timing prior to stimulation but did exhibit behavioural dif-

ferences subsequent to stimulation. If the suggestion that PWS demonstrate similar behavioural performance as a result of re-organisation is plausible, then PWS should exhibit compensatory neural activity in regions associated with external timing of movement that are specifically compensating for deficits in the internal timing of movements. This indeed appears to be the case as both the cerebellum and the right inferior frontal gyrus seem to be compensatory regions in stuttering; both appear to be associated with timing, and both may specifically be compensating for deficits in the BG's control of timing tasks. Although speculative, this strongly suggests that the compensatory response to stuttering that occurs during speech is occurring as a result of deficits in the ITN. It perhaps explains why, in some studies at least, PWS have not shown differences in asynchrony (the difference in time between taps and the pacing signal) or variability (in the time between taps) on tapping tasks compared to PWDS. However, any failure to find a difference between these groups may also be attributed to task related effects such as the motoric or temporal complexity.

Many of the behavioural studies investigating timing abilities in PWS employed simple motoric and temporal tasks. Tapping at isochronous intervals is, as a task, relatively easy and this ease may explain a lack of differences in behavioural performance between PWS and PWDS, a problem that may extend to differences in regional brain activation in neuroimaging studies. Imaging data from early research on finger movements shows that the amount of cerebral blood flow to a particular region depends upon the complexity of the task (Shibasaki et al., 1993). Therefore, simple tasks are not sufficiently motorically demanding to engage parts of the brain normally employed in more complex tapping tasks and which are impaired in PWS. This principle has been demonstrated experimentally in a number of studies. For

example, Zelaznik et al. (1994) failed to find behavioural differences when comparing unimanual tapping performance, but successfully found differences in the same group of stuttering participants when examining bimanual tapping at an isochronous interval (Zelaznik et al., 1997). Similarly, increasing the syntactic complexity of words surrounding a to-be-repeated phrase, decreased speech motor stability for PWS as compared to PWDS (Kleinow and Smith, 2000).

In the same way that increasing the difficulty of the motor movement associated with the task could better reveal differences (should they exist) in behavioural performance and neural activation, so too could placing more strain on the systems governing temporal control of movements. Whereas Webster (1985) failed to find a difference in behavioural performance for PWS during bimanual tapping in a 1:1 ratio (that is one tap of the right hand for every tap of the left hand), Webster (1990) found that PWS took a substantially longer time to tap the required number of times when tapping in a ratio of 2:1 (that is two taps of the left hand for each tap of the right hand) than PWDS. Tapping at an uneven ratio (2:1) places significantly more demand on the neural systems governing timing than does tapping in an even ratio (1:1). This suggests that PWS are much less efficient in coordinating motor output to complex temporal patterns. Similarly, Lewis et al. (2004) demonstrated that parametrically increasing the number of different intervals in a series of tones resulted in a corresponding increase in neural activation in regions associated with timing. These studies show that, increasing the demands on temporal processing is more likely to yield differences in behaviour and by extension, in neural activation. This is particularly relevant in the case of speech since speech is rarely perfectly isochronous but rather quasi-periodic (Martin, 1972). Speech contains multiple lev-

els of temporal complexity (Goswami and Leong, 2013; Kotz and Schwartze, 2010) and is therefore substantially more demanding than tapping at an isochronous interval or in a 1:1 ratio. That is to say, differences in the complexity of rhythms required for speech and finger tapping may explain why most timed movements are relatively normal in PWS. Additionally, the timing required for speech control is robust to interference so difficulties in timing movements or speech may only become evident under increased cognitive loads (e.g. Saltuklaroglu et al., 2009). If PWS were compared to PWDS on a tapping task that contained a similar degree of temporal complexity usually required by speech, then clinically meaningful differences in behaviour are likely to emerge. While there is a theoretical distinction between motor and temporal complexity, in practise, this distinction may not be so clear. Using near infrared spectroscopy (a means to measure the level of deoxygenated blood from the scalp somewhat analogous to how fMRI measures neural activity) Koenraadt et al. (2013) found that that the two may not be mutually exclusive. Tapping at multiple frequencies activated larger portions of the motor cortex than tapping at single frequencies. The extent to which manipulating motoric and temporal complexity are able to elicit behavioural differences in timing between PWS and PWDS remains to be tested by future research. Yet, even if these tasks are unable to elicit such differences in PWS, future research investigating the overlap between stuttering and timing should consider the use of neuroimaging techniques.

6.8 Directions for future research

There appears to be a vast gap in the stuttering literature particularly with respect to neuroimaging and brain stimulation of timing tasks. In particular, I know of no fMRI or PET studies that specifically examined internally or externally timed movements in PWS using either simple or complex temporal intervals despite the long theoretical history of an association between deficient timing and stuttering. The timing deficits I propose to exist in PWS are only tentative suggestions and remain to be verified by future research. Our proposal can nevertheless be used to generate a number of testable hypotheses. For example, it could be hypothesized that PWS show impaired behavioural performance and corresponding neural activation in tasks that require the internal timing of movements (the continuation phase of a finger tapping task) as opposed to the external timing of movements (the synchronisation phase of a finger tapping task)

Likewise to the best of our knowledge, there are no studies investigating neural oscillations in PWS in response to isochronous or non-isochronous tones either by passive listening, finger tapping or vocalisations. Given the role of neural oscillations in timing (Arnal and Giraud, 2012), it would be interesting to investigate how they might differ between PWS and PWDS in the context of a timing task. With respect to studies of brain stimulation, no studies have yet examined the effect of disruptive TMS on the right inferior frontal gyrus, the SMA or the cerebellum in PWS in a timing task. Although speculative, it might be expected that tapping in time to a metronome (external timing) will be relatively unimpaired because PWS can rely on the cerebellum and premotor cortices much in the same way as non-stuttering adults

do. However for self-paced tapping it might be expected that following inhibitory TMS to the right inferior frontal gyrus, PWS will be significantly impaired because they cannot rely on either the right inferior frontal gyrus or the BG. In contrast, PWDS will be able to rely on the BG, but not the right inferior frontal gyrus. The compensatory function of the right inferior frontal gyrus in stuttering is biologically plausible in that it forms part of a core timing-network (Wiener et al., 2010), is functionally interconnected with the basal ganglia (Kung et al., 2013) and is utilised for the processing of speech rhythm (Geiser et al., 2012).

While this article focused on the neural correlates of the ITN and the ETN during the perception and production of rhythmic movements and stimuli, there are many other tasks that probe these networks. The finger-tapping task is a continuous task that is often conducted in the presence of a regular external stimulus. It is possible that the regular external stimulus reduces behavioural variability and (possibly the associated) neural activity much in the same way that it is able to temporarily induce fluency in PWS. It would therefore be prudent to examine the timing abilities of PWS on tasks that do not contain such regular stimuli or where there is a disruption to the external stimuli. In line with the hypothesis of impaired internal timing and the hypothesized compensatory increases in regions associated with the processing of external timing of movements, it might be expected that PWS are more reliant on external cues. As such it would be interesting to test abilities of PWS to judge whether a 'test interval' is longer or shorter than a 'reference interval' and how these judgements are influenced by the presence of a 'distractor interval' that they must ignore (see Rao et al., 2001). To this end, I know of no studies that have examined temporal judgement deficits in PWS either behaviourally or neuro-

logically. More generally, if it is demonstrated that PWS exhibit deficits in timing, it would be particularly interesting to see if there is any dissociation between these different types of timing tasks or modalities; There may for example, be a dissociation between motor timing or judgement duration or between auditory and visual timing.

6.9 Concluding remarks

In conclusion, this chapter provides a theoretical framework with which to view stuttering as a disorder of timing. This paper reviews converging evidence from neuroimaging and brain stimulation experiments showing a great degree of overlap between the structures engaged in the internal timing of movements and the regions thought to be causally involved in stuttering. Evidence of overlap between the neural structures engaged in the external timing of movement and link them with compensatory activity in PWS is also presented. Further emphasis is placed on the significant gaps in the literature and suggest avenues for further research motivated by this overarching theory. More generally, this article highlights anomalies in the functional activations and the structural anatomy of the areas involved in the processing of time in stuttering, that are linked to the dysfluent production of speech and should motivate further research in the field.

Chapter 7

Beta band, Timing and Stuttering

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(see Appendix D for original article)

7.1 Introduction

It has been proposed that one of the causes of stuttering is a deficit in brain timing networks (Alm, 2004; Etchell et al., 2014a; Ludlow and Loucks, 2004). In stuttering, there appear to be structural and functional abnormalities in brain areas (such as the basal ganglia and supplementary motor area) that provide the substrate for internal timing (the ability to time movements without an external cue; Etchell et al. 2014a). There are also structural and functional abnormalities in areas (such the cerebellum and premotor cortex) linked to external timing (the ability to time movements with an external cue), which are thought to represent compensatory plastic changes in stuttering (DeNil et al., 2008; Lu et al., 2012; Watkins et al., 2008). Currently, it remains unknown whether such deficits in internal timing mechanisms in stuttering may be manifest in any measurable neural marker. One possible candidate is oscillatory activity in the beta frequency band

7.2 The beta band and internal timing

Neural oscillations in the beta frequency band (15-30Hz) are classically related to motor activity (see Kilavik et al. 2013 for review): decreasing in power prior to movement and then rebounding once the movement has finished (Pfurtscheller, 1981). Recently there has been considerable interest in the role beta oscillations might play in the brain's ability to represent temporal information because the observed associations between beta band power modulations and the timing of auditory beats (Arnal and Giraud, 2012; Arnal et al., 2014). These investigations are only in their

infancy but have already produced some intriguing observations. For example, Fujioka et al. (2012) used magnetoencephalography (MEG) to measure beta oscillations while subjects passively listened to sounds at regular (390, 585 and 780ms) and irregular intervals (varying between 390 and 780ms). Whereas the slope of the decrease in beta power after the onset of sounds was identical across conditions, the rising slope of beta power was maximal prior to the onset of the next expected sound for the regular but not the irregular conditions. The authors concluded that modulations in beta oscillatory activity represented an internalisation of predictable intervals between sounds. More recently, Cirelli et al. (2014) replicated these results in an electroencephalography (EEG) study showing a similar pattern of anticipatory beta activity across multiple temporal intervals. Arnal and Giraud (2012) contends that the beta modulation observed in the Fujioka et al. (2012) study may reflect the motor system generating efference copy signals at the tempo of stimulation. Empirical support for this prediction comes from recent work by Arnal and colleagues (2014) who showed that correctly judging whether or not a target tone had been delayed in time was associated with greater cortical beta power before the target tone.

There is good evidence to suggest that beta oscillations in the cortex reflect oscillatory activity originating in subcortical structures. Much of our knowledge of beta oscillatory activity in subcortical regions comes from studies in animals or humans with deep brain implants to treat Parkinson's disease because it is not routinely possible to make such invasive recordings in healthy adults. Nevertheless, the pattern of beta desynchronisation and resynchronisation observed in the cortex during and subsequent to movement can also be observed in the basal ganglia of humans (Brittain and Brown, 2014; Brittain et al., 2014) and macaques (Courtemanche

et al., 2003). MEG experiments indicate the basal ganglia and cortical regions are connected via functional loops (see Jenkinson and Brown (2011)) further suggesting there is a relationship between beta oscillations at different levels of the brain. Consistent with this line of reasoning, Klostermann et al. (2007) reported that in humans, beta band power recorded from the basal ganglia (using depth electrodes) and the scalp (using EEG) during a cued choice reaction time task was correlated in phase and amplitude (measured by magnitude-squared coherence). Likewise, it has been demonstrated experimentally that the cortex and the subthalamic nucleus exhibit beta band amplitude and phase coherence, and it is hypothesized that such an interaction relies on the striatum (Hirschmann et al., 2011).

The relationship between cortical and subcortical beta oscillations, together with the fact that beta oscillations in the motor and auditory cortices are related to internal timing (Fujioka et al., 2012), suggests that beta oscillations in the striatum might also be related to internal timing. Accordingly, Bartolo et al. (2014) examined the role of beta oscillations in timing by recording local field potentials from microelectrodes implanted in the putamen of healthy macaques during a synchronisation and continuation task. This task requires that the macaques tap in time with a beat (the synchronisation phase) and that they continue to tap once the beat has been removed (the continuation phase). Whereas the synchronisation phase is an index of external timing (due to the presence of an external stimulus), the continuation phase is an index of internal timing (due to the absence of an external stimulus; Teki 2014). The main finding from the Bartolo et al. (2014) study was that beta activity was strongly biased to the continuation phase as opposed to the synchronisation phase of the task indicating that putamenal beta oscillations are tuned to internal rather

than external timing of movement.

There is evidence that beta oscillations can be recorded from the striatum during self-paced movements in humans. Intracranial recordings from the putamen of an epileptic patient showed that beta power peaks near the onset of self-paced bimanual finger extensions (Sochurkova and Rektor, 2003). While not focusing directly on beta oscillations, there is evidence from functional neuroimaging to implicate the striatum in internal timing in healthy adults. For example, Grahn and Rowe (2013) demonstrated that the putamen responds to the detection of regularity rather than the detection of beats, suggesting that it is involved in internally paced movement rather than simply the detection of the presence or absence of a beat. The basal ganglia are also more active during subjective judgments of temporal intervals relative to judgments of externally timed intervals (Coull et al., 2013) and the putamen shows greater activity during continuation tapping but not synchronisation tapping as compared to rest (Rao et al., 1997). Interestingly, individuals with bilateral lesions to the basal ganglia perform poorly on the continuation but not the synchronisation phase of a rhythmic tapping task (Coslett et al., 2010). Such evidence suggests that the putamen is essential for internal timing.

7.3 The beta band and stuttering

What are the implications of these results in the context of stuttering? If indeed stuttering is a disorder of internal timing (Alm, 2004; Etchell et al., 2014a), and if beta oscillations in the basal ganglia are involved in internal timing (Bartolo et al., 2014) and/or the cortex (Cirelli et al., 2014; Fujioka et al., 2012) then it follows

that stuttering could be a disorder caused by striatal abnormalities that result in abnormal beta power. More specifically, stuttering could be a disorder in which beta power is hypoactive or where the relationship between cortical and subcortical beta power is unstable. That there are exaggerated beta band responses in adults who stutter (AWS; Rastatter et al. 1998) and reduced beta band responses in children who stutter (CWS; Özge et al. 2004) provides some evidence for this contention. The suggestion that stuttering is a disorder caused by abnormalities of the striatum is consistent with neuroimaging studies of CWS. Investigating differences in brain structure and function of CWS is valuable because they have had much less time to react to stuttering as compared to AWS. Due to the young age of the population, any differences observed between CWS and children who do not stutter (CWDS), are more likely to reflect anomalies related to the cause of stuttering rather than consequences of stuttering (see for review Etchell et al., 2014a; Chang and Zhu, 2013; Sowman et al., 2014). The striatum is involved in the articulatory control of speech at different rates (Riecker et al., 2005, 2006; Wildgruber et al., 2001) and in speech rhythm (Fujii and Wan, 2014) and research shows CWS exhibit reduced levels of connectivity between the putamen and several cortical structures including the supplementary motor area, superior temporal gyrus and inferior frontal gyrus (Chang and Zhu, 2013). CWS also have less grey matter in the left putamen (Beal et al., 2013) than CWDS. Interestingly one study reported CWS exhibit reduced levels of beta band activity at rest in the cortex compared to CWDS (Özge et al., 2004).

If abnormal beta power arising from the striatum is causally related to stuttering, then fluency inducing manipulations should normalise beta power. This con-

tention is supported by functional neuroimaging and electrophysiological studies. The finding that putamenal beta band oscillations are biased towards internal timing (Bartolo et al., 2014), together with the fact that the putamen responds to regularity (Grahn and Rowe, 2013) and is known to exhibit beta band oscillations (Sochurkova and Rektor, 2003), suggest that the striatum tracks regular sounds via modulation of beta activity. An fMRI study has shown that AWS exhibit less activation of the basal ganglia during normal speech compared to rest, but that when speaking in time with regular sounds, the level of basal ganglia activation is comparable to adults who do not stutter (AWDS; Toyomura et al. 2011). Given the positive relationship between BOLD activity and beta band responses (Laufs et al., 2003), the normalisation of striatal activity may perhaps be accompanied by normalisation of beta band activity. Additionally, since regular sounds influence cortical beta power (Cirelli et al., 2014; Fujioka et al., 2012) and cortical beta is associated with subcortical beta oscillations (Jenkinson and Brown, 2011; Klostermann et al., 2007), it is likely that regular sounds also influence beta power in subcortical structures. There is evidence that delayed auditory feedback, another fluency inducing mechanism, alleviates cortical beta band abnormalities in AWS. Rastatter et al. (1998) used EEG to show that AWS exhibit hyperactivity of the beta band in the cortex when reading aloud. This hyperactivity was markedly reduced by delayed auditory feedback. In the same way that a metronome affected the haemodynamic response in cortical and subcortical structures (Toyomura et al., 2011), delayed auditory feedback might have also affected beta band oscillations in both cortical and subcortical structures. Indeed most fluency inducing mechanisms seem to work by facilitating coupling between auditory and motor systems as well as the putamen (Stager et al.,

2004).

It is unclear whether the hyperactivity of the beta band activity in stuttering (Rastatter et al., 1998) reflects causal or compensatory mechanisms. Since the volume of white matter and beta band amplitude increases with age (Uhlhaas et al., 2010) and because the density of the white matter fibres underlying the motor cortex and superior temporal areas were negatively correlated with the severity of stuttering (Cai et al., 2014b). It is our opinion that the hyperactive beta oscillations in the cortex reported in Rastatter et al. (1998) may be compensating for hypoactive beta oscillations in the basal ganglia. Delayed auditory feedback may have normalised the beta band oscillations in the basal ganglia thereby reducing the need for compensation via hyperactive beta in the cortex. This idea suggests both AWS and CWS should exhibit reduced beta band responses in the putamen when internalizing rhythms. The fact that fluency-inducing mechanisms reduce the hyperactivity of the beta band in the cortex has major implications for stuttering. Firstly, it implies that without regular external stimulation, AWS have abnormal beta oscillations in the cortex and possibly the striatum. Secondly, normalising compensatory hyperactivity in the cortex as well as temporarily alleviating stuttering implies that delayed auditory feedback may act to normalise hypoactive oscillations in the striatum.

In summary, if stuttering is a disorder of internal timing and internal timing is represented by modulations of oscillatory power within the beta band in the striatum, then it is likely that the cause of stuttering is reflected in abnormal beta band oscillations in the putamen. This is consistent with the structural and functional abnormalities in CWS (Chang and Zhu, 2013; Beal et al., 2013), the notion that

beta band oscillations are evident in the putamen (Sochurkova and Rektor, 2003) and that CWS exhibit beta band abnormalities (Özge et al., 2004). The idea that beta oscillations reflect the neural abnormality causing stuttering is further supported by the observation that fluency-inducing mechanisms normalise activity in the putamen (Toyomura et al., 2011) and also beta power in the cortex (Rastatter et al., 1998). Future studies should thoroughly investigate beta oscillations in stuttering.

Chapter 8

Dynamic Causal Modelling of Beta Band in Adults

8.1 Introduction

Nearly everything we do as humans involves some sort of timing. Accordingly, there has been a vast amount of research devoted to studying the neural substrates of timing. In the laboratory setting, the most frequent paradigm used to investigate timing abilities is the paced finger tapping task (Stevens, 1886). This typically involves participants coordinating their taps such that they are in time with an auditory or visual beat (synchronisation). Sometimes, however, participants are required to coordinate their taps so that they occur in between the pacing stimuli (syncopation). Interestingly, while most individuals are able to synchronise their taps to regular beats, they have much greater trouble syncopating their taps to rhythmic beats. Given the identical auditory stimulus and rhythmicity of motor movements in both conditions, this begs the question of why.

Over the years, a wide variety of cortical and subcortical regions including, but not limited to, the supplementary motor area, basal ganglia, cerebellum and right inferior frontal gyrus have been implicated in both synchronised and syncopated tapping (see Wiener et al., 2010). In particular, a much broader network of regions tends to be active during syncopation as compared to synchronisation (see Jantzen et al., 2004; Mayville et al., 2002). It goes without saying that these regions do not operate in isolation. They interact with one another. In other words, the difficulties associated with syncopated finger tapping may be related to how particular regions of the brain communicate with one another. One mechanism by which cortical regions interact is via neural oscillations (see for review Fries, 2005).

Neural oscillations refer to fluctuations in the excitation or inhibition of pop-

ulations of neurons and can be observed across all levels of the brain (Thut et al., 2012). Neural oscillations are often described according to the frequency at which they occur and are important because they enable communication between distant regions of the brain (Engel et al., 2001). In addition to this, neural oscillations tend to be associated with specific functions. For example, the alpha band first observed by Hans Berger is associated with sleep whereas the gamma band is often associated with working memory. Due to their inherent regularity, it has been suggested that neural oscillations could be exploited for predicting when events will occur (Buzsáki and Draguhn, 2004; Engel et al., 2001; Fries, 2005). Beta band oscillations are traditionally associated with motor movement. Modulation of beta band activity is observed when executing rhythmic motor movement, but not when listening to acoustic stimuli (Boonstra et al., 2006). Recent theoretical work by Arnal and Giraud (2012) suggests that the beta band (15-30Hz), classically associated with motor movements (Burianová et al., 2013; Kilavik et al., 2013), may be particularly important for timing.

This idea has been tested more formally through a series of MEG and EEG experiments (Fujioka et al., 2012; Arnal et al., 2014). Fujioka et al. (2012) used MEG to examine how the auditory and motor regions interact when an individual is passively listening to an isochronous rhythm with particular focus on the beta band. In this study, participants listened to a train of isochronous intervals of either 390, 585 or 780ms, or intervals that varied randomly between 390 and 780ms, without making overt movements. Time frequency analysis revealed an immediate decrease in beta band power 200ms after stimulus onset. The magnitude of the decrease was nearly identical across all conditions. However, the rising slope of the following beta band

resynchronisation (beta rebound) was modulated according to the rate of isochrony and always peaked before the next expected stimulus. In the random condition, the rebound occurred significantly earlier than any of the regular conditions. This pattern was evident in a variety of regions including but not limited to the SMA and the right inferior frontal gyrus (Wiener et al., 2010), as well as the auditory and motor cortices. This provides strong evidence suggesting there are interactions between sensory (auditory) and motor regions and that these interactions may be used to predict the occurrence of upcoming stimuli. More recently, Cirelli et al. (2014) used the same paradigm in conjunction with EEG to compare the beta band response of adults and school-aged children. The authors reported that for both adults and children, beta band power was maximal before the onset of the sound and synchronised between the auditory and motor cortices. Additionally, for children, the effect was weaker for faster rates of stimulation. In a related experiment, Arnal et al. (2014) compared beta band activity while participants judged whether a single tone in a stream of other tones was presented earlier or later than normal. They found that beta power was maximal for correct but not incorrect judgements, suggesting that interactions between the auditory and motor cortex in the beta band are used to facilitate judgement of time. More recently, Bartolo et al. (2014) measured beta band oscillations from the putamen of macaques during a synchronisation continuation task. They demonstrated that the beta band was biased towards the continuation phase of the task indicating that it was somehow related to internal timing.

The significance of the motor activity in these passive listening tasks (see also Grahn et al., 2007; Grahn and Rowe, 2009) is particularly interesting and can be related to a fundamental neurophysiological phenomenon commonly referred to as

efference copy. An 'efference copy' is a copy of a motor command that propagates to the sensory regions of the brain which enables a person to distinguish sensory input that results from their own movements (reafference) from sensory input that results from the movements of others (exafference). This is achieved by minimizing the sensory consequences of one's own action in contrast to the actions of others which are usually unpredictable (Crapse and Sommer, 2008).

A number of groups (e.g. Arnal and Giraud, 2012; Arnal, 2012; Arnal et al., 2014), have proposed that such efference copies, generated by the motor system when tapping to a beat, are also generated when a person is passively listening to a beat. This work builds on the fact that individuals tend to synchronise movements with isochronous beats and that modulation in beta activity (related to motor movement) can be observed even in the absence of movement (Fujioka et al., 2012; Cirelli et al., 2014). Arnal's group contends that the form of anticipation used to predict the sensory consequences of one's own movements could also be used to predict the consequence of a predictable external event. Given their role in prediction, efference copy signals could be exploited to predict the occurrence of an upcoming sound by narrowing the time window in which the sound can be expected in the auditory cortex. More specifically, he argues that efference copies transmitted in the beta band predictively constrain activity in the auditory cortex (Arnal and Giraud, 2012; Arnal, 2012; Arnal et al., 2014). However, in the absence of direct experimental evidence and statistical analyses that allow for inferences about the direction of causal influences in the beta band, such interpretations remain untested.

One means by which to examine causal interactions between the auditory

and motor cortices is by using dynamic causal modelling (DCM). In brief, DCM aims to find the network and connections between regions of the brain that explain the data as accurately as possible with the least amount of complexity (van Wijk et al., 2013). DCM was originally developed for fMRI, but has since been applied to evoked responses for EEG and MEG data. More recently, DCM has been extended to induced responses. In the context of the frequency domain, DCM allows investigation of how changes in a given frequency in one area of the brain influence the same or different frequencies in another area of the brain (Chen et al., 2008).

In this experiment, DCM was applied for induced responses to synchronised and syncopated finger tapping in order to elucidate the directionality of the interactions between the auditory and motor cortex. Accordingly, it was hypothesized that if the beta band was only related to motor activity, then the time frequency responses in the motor cortex would be identical across conditions whether or not there was a coincident auditory stimulus. In contrast, if beta band activity was influencing or being influenced by auditory activity, then one would expect beta band oscillations to differ between experimental conditions. The fact that a much broader network of regions is active during syncopation as compared to synchronisation implies the later condition places demand on the systems governing timing and communication between these areas. It was therefore expected the syncopation phase of the task to place greater demand on internal timing than the synchronisation phase of the task, as indexed by greater beta band activity. Based on the assumption that beta band power indexes the degree of internal timing for a given task (Etchell et al., 2014b; Teki, 2014), it was also expected that there should be greater beta band activity for the both continuation phases as compared to their respective pacing conditions.

While informative, the analyses of specto-temporal data alone does not permit inferences about the directionality of causal relationships. Therefore, it was hypothesized that if the motor cortex was exerting influence over the auditory cortex in the beta band (rather than vice versa), then the pattern of induced responses would be best explained by a DCM containing backward connections (i.e. propagating from motor to sensory areas). The difference between pacing conditions should, in accordance with the time frequency data, be best explained by DCM containing backward connections.

8.2 Method

8.2.1 Participants

Eighteen adults (eight females; mean age: 28 ± 4.5) gave informed consent and participated in the study for monetary compensation. All reported right-handedness and normal hearing before the experiment. None reported any history of neurological disease or mental illness. No participant was on medication or had a history brain injury. Two participants were excluded from analysis due to poor behavioural performance (i.e. not complying with the instructions for the task or performing poorly on one of the two conditions), one due to technical problems and three due to low signal to noise ratio. This left a total of 12 subjects for analysis. This study was reviewed and approved by the Human Research Ethics Committee of Macquarie University (see Appendix E for final approval)

8.2.2 MEG Acquisition

Neuromagnetic responses of participants were recorded with whole head MEG. The MEG system (Model PQ1160R-N2, KIT, Kanazawa Japan) consisted of 160 coaxial first order gradiometers with a 50mm baseline (Kado et al., 1999; Uehara et al., 2003). Prior to MEG measurements, five marker coils were placed on an elasticised cap on the participant's head. The head-shape and fiducial points (bilateral preauricular points and the naision) were recorded with a pen digitizer (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing marker coils in the MEG dewar both before and after the recording session. The total amount of head movement was calculated by subtracting the position of each marker coil prior to the experimental task from their position at the end of the experimental task. No participant was discarded from analysis due to excessive (>7mm) movement During recording, MEG was continuously sampled at 1000Hz and band-pass filtered between 0.03 and 200Hz. Participants lay supine with their arms by their sides.

8.2.3 Behavioural Task

Participants completed two tasks in the experimental session requiring them to either tap with the beat (synchronisation) or tap between the beats (syncopation). Participants responded by tapping their right index finger on a pneumatic tapping pad ($http://www.curdes.com/hhsc-1x1-tp.html$). A visual cue (lasting for 1000ms) signalled which form of tapping (either synchronisation or syncopation) was to be performed. In each trial, participants were presented with a total of 48 tones (60ms, 1000Hz), separated by a constant interval of 800ms (equivalent to a stimulus rate of

1.25Hz). After 24 tones had been played (pacing condition), the tones were removed and the participant was required to continue tapping as though the tones were still on (continuation). After both phases of the tapping task) a single 1000ms long tone (1000Hz) was played signalling the end of the trial. In the synchronisation condition, participants were instructed to coordinate their taps such that they occurred as close as possible to the beat. In the syncopation condition, participants heard the same stimuli but were instead required to coordinate their taps such that they occurred as close as possible to the middle of the two beats (rather than on each beat as in the previous condition). After one synchronisation and one syncopation trial, participants rested for a random duration of time ranging from 15 to 20 seconds during which ongoing baseline activity was recorded. Overall, there were a total of 24 synchronisation trials and 24 syncopation trials (or a total of 288 sounds per condition). The total duration of the experiment was 40 minutes. Sounds were presented through a (Panphonics) positioned at the feet of the participant and played at 75dB sound pressure level (as measured from the head of the participant in the dewar). All stimulus sequences were presented on a Dell Pentium 4 computer running Windows 7 using Presentation 16.3 (Presentation Neurobehavioural Systems, Albany USA).

8.2.4 Behavioural Data

The time point of each response was defined as when a participant's finger came into contact with the tapping pad. Missed trials (no tap occurring between -400ms and 400ms of the stimulus) and trials containing multiple taps (within -400ms and 400ms of the pacing signal) were excluded from analysis. For all conditions, three measures

performance were calculated. The mean and standard deviation of the asynchronies were included for ease of comparison to previous studies. Additionally, the mean absolute deviation (MAD) of the asynchronies was calculated. The MAD of the asynchronies was included because the classically used mean of the asynchronies is insensitive to taps that occur at positive asynchronies. For example, if half of the taps occurred at 400ms before the onset of the sounds and half the taps occurred at 400ms after the onset of the sound, the mean of the asynchronies would cancel out to give 0ms, but the MAD of the asynchronies would provide a value of 400ms.

8.2.5 MEG Pre-processing

All MEG data was pre-processed using the SPM8 toolbox in MATLAB. Data were down-sampled to 250Hz, bandpass filtered between 0.25 and 40Hz and a stopband filter (48 to 52Hz) applied to suppress line noise. When epoching the data, each condition was time locked to the onset of the response. Eyeblinks were modelled out from all trials for each individual participant using inbuilt artefact rejection tools in SPM. This procedure models a typical eyeblink based on a data from given sensor (in this particular case, the sensor closest to the right eye was selected) and subsequently removes that portion of data from all trials and conditions.

8.2.6 Functional Localizers

A similar method of analysis to Arnal et al. (2014), who examined the role of the beta band in a prediction task, was employed. The full details of the procedure used to localise sources is described in the aforementioned publication. Here, I detail the

slight differences in how sensors were selected. Specifically, a cluster of five sensors along a central area that contained largest amplitude within 50ms in response to a randomly spaced button press was selected. These central sensors were thought to reflect activity underlying the motor cortex. A topographic map of the sensors can be seen in Figure 8.1. Unless otherwise stated, analysis is conducted on this sensor selection.

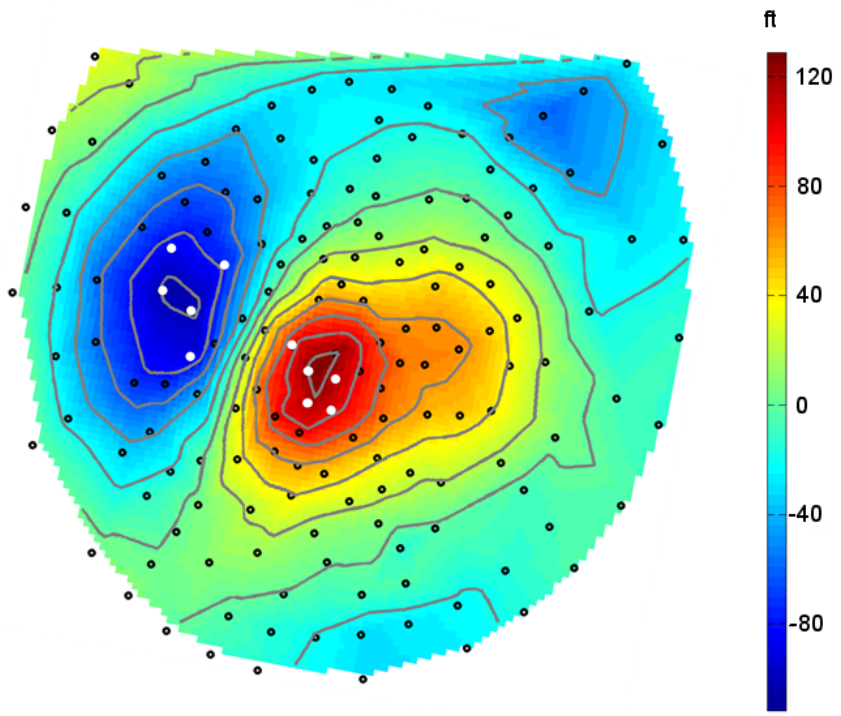

Figure 8.1: Topographic map of motor evoked response. Shows the grand mean (N=16) of the evoked data 32ms after a randomly paced button press using the right hand. The white dots indicate the sensors with the maximum amplitude.

8.2.7 Time-Frequency Analysis

A time frequency analysis was then conducted from 1 to 40Hz and between -800ms and 1000ms on each of the three dipoles (left motor and bilateral auditory dipoles) using a Mortlet transformation. The spectra plots of the induced activity were

then cropped in the time domain from -500ms to 800ms to avoid edge artefacts and rescaled according to the mean frequency over the entire epoch. Averages were taken across channels in each dipole (i.e. 10 channels for each dipole). SPM for MEG uses Random Field theory to correct for multiple comparisons across three dimensional space. For induced data this consists of a 2D representation of the induced field for each sample of the time dimension between -500ms and 800ms around stimulus onset. These statistical parametric maps (SPM) were then submitted to the second level of SPM analyses. Paired t-tests were performed between each pacing condition and its respective continuation condition (i.e. (synchronise vs continue-nize and syncopate vs continue-pate)) as well as between each type of pacing (i.e. synchronise vs syncopate and continue-nize vs continue-pate). Each (SPM) contained a cluster of more than 20 supra threshold voxels at a strict threshold (0.05 false-discovery rate (FDR) corrected and a more relaxed threshold $p<0.001$ uncorrected). Furthermore, since the experiment was focused on examining differences in synchronisation and desynchronisation, two such maps were calculated for each contrast for which the dependent variable was the level of beta band modulation.

8.2.8 Dynamic Causal modelling Analyses

DCM, is at its core, a measure of 'effective connectivity' and as such, is concerned with how changes in one brain region cause changes in another as a result of manipulating experimental conditions (Chen et al., 2008). Importantly, the goal of DCM is not to fit the data as accurately as possible, but rather to compare the evidence for a set of models, each of which represent a different hypothesis (van Wijk et al.,

2013). Unlike the DCM for evoked response, which are based on neural mass models, the DCM for induced responses relies on simpler linear equations (akin to those used in DCM for fMRI albeit without the haemodynamic responses). In the context of DCM for induced responses, these causative changes are primarily concerned with an increase or decrease in frequency specific power that has been recorded electrophysiologically (Chen et al., 2008; Kilner et al., 2005). More specifically, induced DCM allows one to quantify how changes within a given frequency at one source influence the power of either the same (linear coupling) or different frequencies (non linear coupling) at another source. These connections can further be classified as forward, backward or intrinsic connections depending on whether they originate from and where they terminate. Forward connections originate in lower level sensory areas and target higher level areas. In contrast, backward connections originate in these higher level areas and target lower level sensory areas. Finally, intrinsic connections occur within a particular region and target that same region. Although it is often ignored, the directionality of these linear non linear and intrinsic connections is considered essential for neural functioning (van Wijk et al., 2013). Directionality (or causality) relies not only on temporal precedence (which region is active first), but also how and when the model or system is perturbed by stimuli (Stephan et al., 2010). Effective connectivity (statistical correlations between activations with directionality) is defined as the directed influence one region has over another (Friston, 2009). In brief, in the DCM framework, causality refers to the rate of change in neural activity with respect to time in response to an incoming signal (Kahan and Foltynie, 2013) and the impact of one region on another is quantified by the delay in time (utilising the principles of ?dynamical systems theory?) (Daunizeau et al.,

2011a,b). It is important to note that the DCM approach determines the effective connectivity via arbitrating between various competing models (determined a priori) that express different possibilities in regard to directionality of connectedness. DCM attempts to identify the most plausible model that explains the generation of the observed signal rather than directly analysing the signal. For a review of DCM, see Daunizeau et al. (2011a) and for a more detailed discussion on "what is causal about DCM" see Stephan et al. (2010).

8.2.9 Sources for DCM analysis

While the auditory cortices are often localised using peak amplitudes of N1 or P1 components, the data also included motor activation. For the sake of consistency, it was determined apriori to localise the three different sources in Montreal Neurological Institute and Hospital (MNI) space based on peak activations in previous studies of finger tapping. Because structural MRI scans were not obtained for each individual, template brains were used for source localisation which is a procedure adopted by many researchers (see Brett et al. 2002). The MNI coordinates taken from Witt and Stevens (2013) for the motor cortex were (-36, -21, 54) who also conducted a DCM study of paced and unpaced finger tapping. The locations of the auditory cortices were taken from Jantzen et al. (2004) who conducted an fMRI study comparing paced and unpaced synchronisation and syncopation tapping. The MNI coordinates for the left and right auditory cortices were respectively (-47, -22, 11) and (53, -21, 15).

8.2.10 DCM Model Construction

A total of four DCM models were constructed by imposing constraints over the left motor cortex and the bilateral auditory cortices. In brief, all linear (forward, backward and intrinsic) connections were tested. In each of our models the A matrix, which specifies the connections that are common for both trial types, was identical. In contrast to this, the B matrix, which specifies condition dependent changes in coupling strength, was varied across the different models that were tested. Accordingly, Model 1 contained modulation of both bottom up and top down connections between the auditory and motor cortices (denoted as Bforward/backward). Model 2 contained modulation of bottom up (forward connections) from the auditory to the motor cortices (denoted as Bforward). Model 3 contained modulation of top down (backward) connections from the motor to the auditory cortices (denoted as Bbackward). Model 4 contained no modulation (B0). Each model also respected a number of basic features, namely that 1) the auditory stimulus input was in the left and right auditory cortex at the bottom of the hierarchy 2) The left motor cortex was situated at the top of the hierarchy 3) Intrinsic connections are connections in which the frequencies in one source affect the same (or other frequencies) within itself. Although it is generally recommended to model intrinsic connections as non linear (SPM8 Manual), this study was only interested in the beta band. Therefore, each model contained all intrinsic connections that were modelled as linear. A diagrammatic representation of the models used in this study can be seen in Figure 8.2.

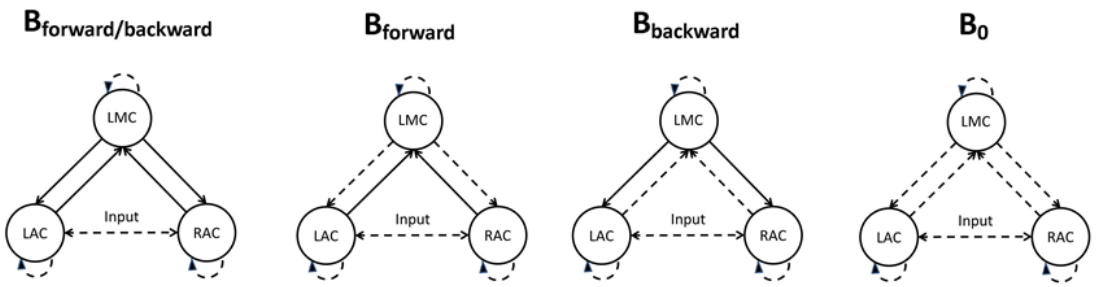

Figure 8.2: DCM models. The dotted lines represent connections between regions and the solid lines represent connections that are allowed to vary between conditions. B0 contains no modulation. B forward contains modulation from the auditory to the motor cortex (but not vice versa). B backward contains modulation from the motor cortex to the auditory cortex (but not vice versa). Bforward/backward contains modulation from the auditory to the motor cortex and vice versa.

The DCM analysis focused on induced components occurring between 0 and 800ms relative to the onset of the response and between 15 and 30Hz for the beta band. The analysis was time locked to the responses rather than the sound so as to determine the types of connections that best characterised the data at the time of the response. However, continuation trials were not included in the DCM analysis. This is because DCM requires a stimulus input and there was no such external auditory input in either of the continuation conditions. Restricting the frequency to the beta frequency range ensures that other frequencies do not influence the DCM and therefore allows us to examine the contribution of the beta band to sensorimotor synchronisation in isolation. The given epoch was deliberately chosen so as to encompass the same number of auditory stimuli and motor responses for all conditions such that it was impossible for the models to be biased towards one particular condition or model. For the DCM comparing the pacing conditions to baseline, the between subjects effect was modelled as 0 1. Here, the 0 corresponds to the first condition (resting) which is used as baseline and the 1 corresponds to the pacing

condition and how that is different from baseline. This was based on the relatively intuitive assumption that both pacing conditions would require additional activation/connections than the baseline. Likewise, when comparing the synchronise and the syncopate conditions, the between subjects effect was modelled as 1 0. Here, the syncopate condition is being compared to the synchronisation condition (which is being used as a baseline). This is less intuitive and requires justification. Although there is no clear baseline per se, studies examining differences between synchronisation and syncopation show that tasks involving syncopated beats recruit additional areas to those used in synchronisation. This would mean that modelling the baseline as the synchronisation phase rather than the average of the two conditions is perhaps more appropriate. Three regions were modelled using an equivalent current dipole positioned a priori using MNI coordinates of the extracted sources, informed by the peak activation of previous fMRI studies (see above Jantzen et al., 2004; Witt and Stevens, 2013). Importantly, each of the three regions submitted for the DCM analysis were included in every model. The reason for this was because I was interested in the differences between the types of connections that best described the optimal model (i.e. model space) rather than differences in the explanatory power of different networks (i.e. model parameters).

8.2.11 Bayesian Model Selection

Bayesian model selection (BMS) is a statistical procedure for determining the best model. It estimates the model evidence (i.e. p(y—m) or the probability of the data y given a model m) and is a necessary step in any DCM analysis. The model evidence

is a quantifiable estimate of the degree of parsimony of each model or the model that explains the data of an individual as accurately as possible with the least amount of complexity. Additionally, the model evidence is a measure of how well a given model is able to explain the group data. In the present study, since the cognitive functions underlying finger tapping in the synchronise and syncopate are very basic and should not vary substantially across healthy adults, a fixed-effects BMS was performed at the group level. Since I was primarily concerned with determining the type of connections that characterised optimal model (i.e. model space) and was not concerned with the specific parameters of the optimal model (i.e. model parameters), BMS alone is sufficient to address the hypothesis of interest (Stephan et al., 2010).

8.3 Results

8.3.1 Behavioural Data

During pacing subjects successfully produced both the synchronise and syncopate patterns. The mean and standard deviation of the asynchrony for the synchronise condition was -52.86ms ± 46.65ms and the mean and standard deviation for the syncopate condition was -22.47ms ± 46.66ms. A paired t-test revealed significant differences between mean asynchronies for the synchronise and syncopate conditions. The mean absolute deviation, or the difference in time between the tap and the sound (synchronise) and the difference in time between the tap and the middle of the sounds (syncopate), was also calculated. Notably however, there was no significant difference in the absolute value of the mean asynchronies

8.3.2 Time Frequency Analysis

The grand averages of the time frequency plots for each dipole can be seen in Figure 8.3. Paired t-tests were conducted between the synchronise and continue-nize condition, between the syncopate and the continue-pate condition, between the synchronise and the syncopate condition and the continue-nize and the continue-pate condition. The comparison used an explicit mask between 15 and 30Hz and are summarised in Table 8.1. The table depicts comparisons between conditions with a strict threshold of p=0.05 FDR corrected and a more relaxed threshold of p=0.001 uncorrected with a minimum cluster extent of 20 voxels.

Table 8.1: Summary of differences between conditions for time frequency analysis for the left motor dipole. The threshold for inclusion was 0.001 uncorrected and 0.05 FDR corrected. Note that there was no significant difference between synchronise and continue-nize or between continue-nize and continue-pate (and hence these conditions are not included in the table). N=16

Condition	Cluster Size	Hz	Time (ms)	P value
synchronise > Syncopate	256	20.5	136	0.05 FDR
	284	20	-32	0.05 FDR
	110	27.5	-96	0.05 FDR
	25	18	768	0.05 FDR
synchronise < Syncopate	125	19.5	524	0.05 FDR
	63	17.5	-344	0.05 FDR
Syncopate > Continue-Pate	112	27.5	388	0.001 uncorr
Syncopate < Continue-Pate	38	16.5	-144	0.005 FDR
	35	19.5	792	0.001 uncorr
	27	21	16	0.001 uncorr
	16	27	-104	0.001 uncorr

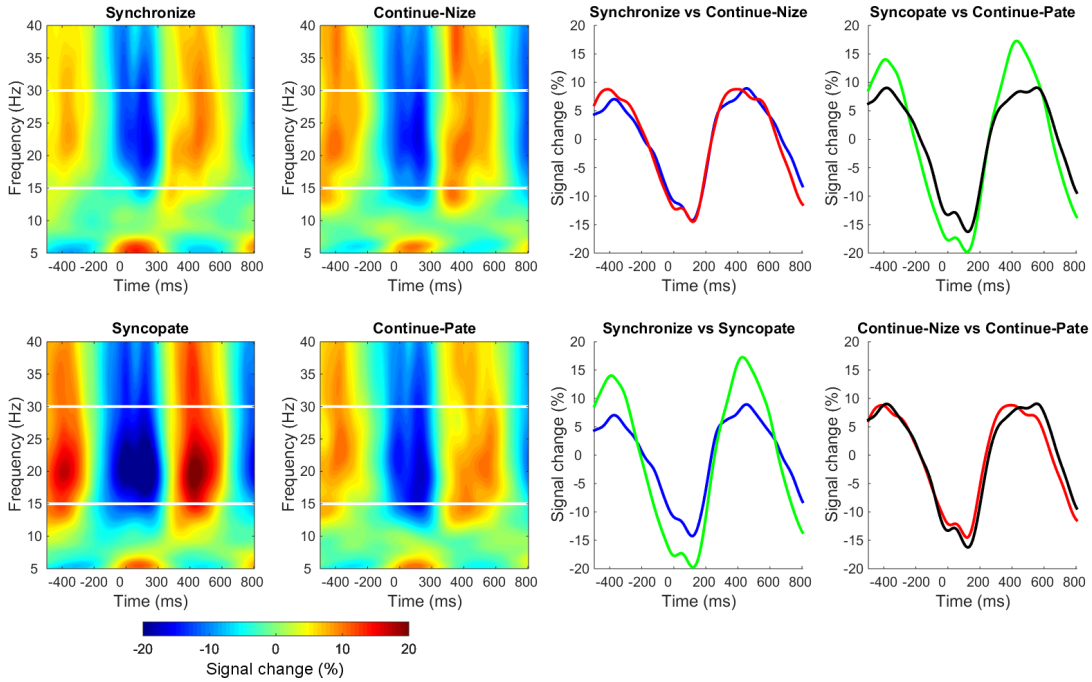

Figure 8.3: Grand mean time frequency plot for the left motor cortex. The first two plots in each row/column show -500ms before and 800ms after response onset between 5 and 40Hz for each pacing and continuation condition (synchronise, syncopate, continue-nize, continuepate respectively). The 15-30Hz ranged is indicated by white horizontal lines in each frequency spectrogram. The last plot in each row/column shows a visual representation of mean intensity across 15-30Hz for the comparison between the respective conditions. The red and blue lines represent the synchronize and continue-nize conditions respectively. The green and black lines represent the syncopate and continue-pate conditions respectively. N=16

8.3.3 Dynamic Causal Modelling Analysis

Visual inspection revealed that there was a good fit between the observed and predicted time frequency responses for both the synchronise and the syncopate conditions (See Figure 8.4). Note that the inbuilt SPM function (spm_dcm_ind_data) normally rescales the observed and predicted responses to the first 1/8th of the induced response and conducts a log transform. This can create what appears to be a very different time frequency plot. Given I had already conducted a time frequency analysis (Figure 8.2), it was necessary to modify the rescaling to determine the accuracy of the source extraction of the DCM, and whether or not it resembled the

data from the motor cortex. The log transformation was removed and the rescaling conducted over the entire epoch based on correspondence with Van Wijk (SPM mailing list $https://www.jiscmail.ac.uk/cgibin/webadmin?A2=spm;492891ec.1410$). There is a clear resemblance between the time frequency responses in Figure 8.2 and the time frequency responses in Figure 8.4 indicating that the sources extracted for the DCM are indeed accurate.

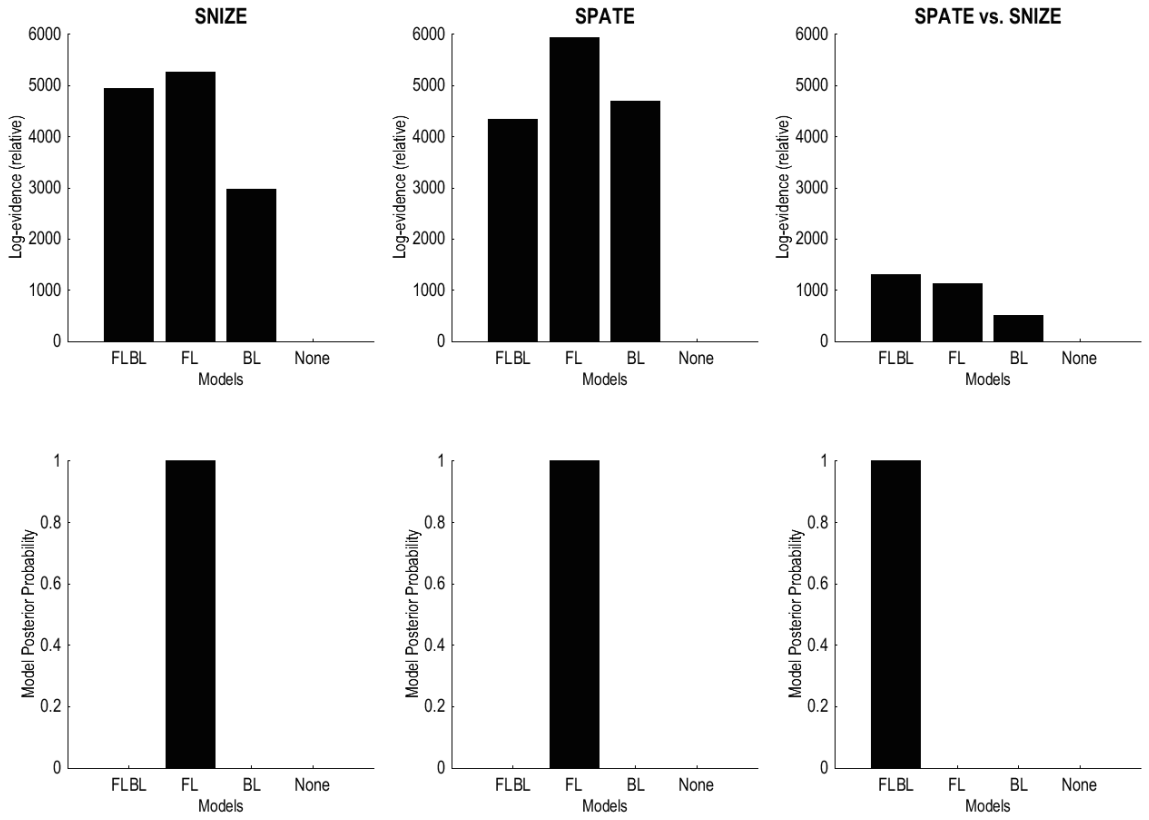

Figure 8.4: BMS Results. The top and bottom rows respectively show the relative log evidence (how well a single model explains a randomly chosen subject) and the posterior probability (how well each model explains the data as a whole) for the comparison of the synchronise and syncopate conditions to baseline. The first and second columns depict the comparison between synchronise and rest and between syncopate and rest while the third column depicts a comparison between syncopate and synchronize. Here syncopate is modelled as requiring at least the same amount of activity as synchronisation plus additional activity/connections. Model 1 = FLBL. Model 2= FL, model 3 = BL and Model 4 = B0. Note that the winning model when comparing the synchronise and syncopate conditions to baseline rest condition is the FL and the winning model when comparing syncopate to the baseline synchronisation conditions is FLBL.

Comparison of the models syncopate conditions revealed that the Bforward/backward model outperformed other models as evidenced by greater relative log evidence and posterior probability. Importantly, difference between the log evidence for winning models and the next best model ranged from 30-300. Usually, a difference in log-evidence of three is taken as strong evidence (Kass and Raftery, 1995) because this corresponds to a model that is twenty times more likely than the alternative or next best model (van Wijk et al., 2013). This difference is analogous to the p=0.05 in classical statistical tests and will emerge at a group level, if and only if the same difference is consistent across individuals (Garrido et al., 2007).

8.4 Discussion

This is the first study to use DCM in conjunction with MEG to investigate the neural networks underpinning sensorimotor synchronisation. This study examined the neural networks underpinning synchronisation and syncopation to an isochronous beat by applying an induced DCM to MEG data. An attempt was made determine the relative involvement of the auditory and motor cortices in different forms of sensorimotor synchronisation. It was expected that if on the one hand, modulations in beta band activity are exclusively related to motor activity, then the absence or presence of a coincident auditory stimulus should have no effect on the profile of the time frequency response at the time of the tap. If on the other hand, beta power is an index of internal timing and not just related to the tap, then there should differences between experimental condition. In line with our expectations, notable differences were identified in the pattern of beta band responses at the time of the

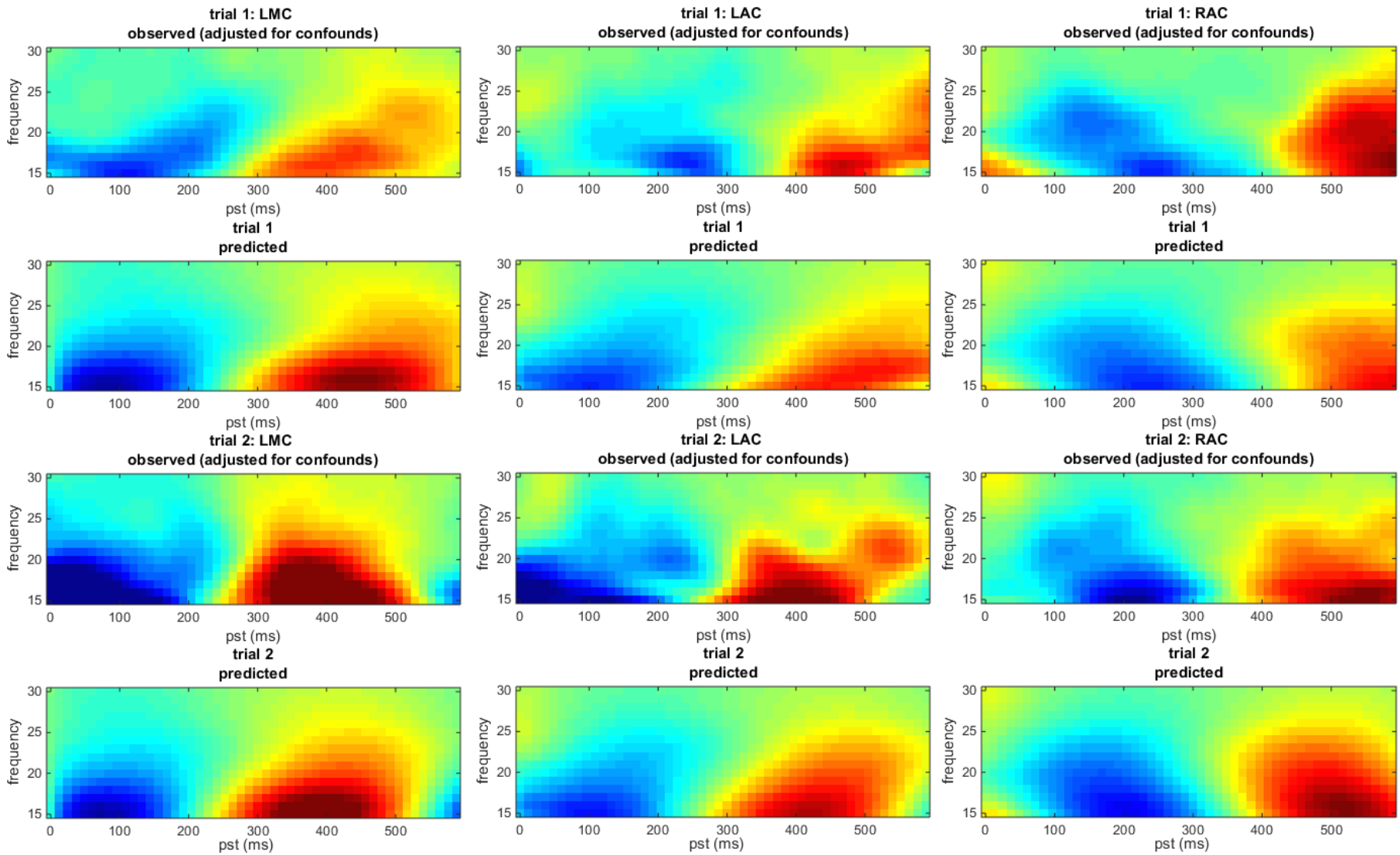

Figure 8.5: Observed and predicted time frequency plots for the winning model of a representative subject. The top two rows show the observed and predicted response for the synchronise condition. The bottom two plots show the observed and predicted plots for the syncopate condition. For this comparison, the synchronise condition was the baseline and the syncopation condition was modelled as the baseline plus additional activity. Note the visual similarity between the observed and predicted plots suggests a good fit of the winning FLBL model.

tap. It was found that the syncopate condition exhibited greater beta power than the synchronise condition and also the continue-pate condition. Additionally, the DCM analysis revealed the profile of responses in the synchronise and syncopate conditions to be characterised by modulation in the forward direction. The difference between the synchronise and syncopate conditions was best explained by a DCM containing modulation in both forward and backward directions.

Before discussing the results of the time frequency and DCM analysis in greater depth it is necessary to show that subjects were able to successfully perform the task. Subjects demonstrated an ability to reproduce both rhythms with relative precision. Notably while there was a significant difference in the mean asynchronies for the synchronise and syncopate conditions, this is not the most valid method of comparison. Whereas the mean asynchronies for the synchronise condition were negative for all subjects, the mean asynchronies for the syncopate condition ranged from positive to negative values. For this reason, a more valid comparison may be to use the mean absolute deviation. Based on this criteria, there was no significant difference between conditions. Our behavioural results are comparable to previous studies that have investigated differences between synchronisation and syncopation at rate of 1.25Hz (e.g. Delignières et al., 2009; Jantzen et al., 2004; Mayville et al., 2002). Since both the synchronisation and syncopation condition contain the same rhythmic stimuli and rhythmic motor movements one would assume that there should be no difference between the synchronisation and the syncopation conditions. This was not the case. Visual inspection revealed a very different pattern of beta band in the motor cortex across our experimental conditions (see Figures 8.2). This was further supported by the results from statistical analysis of the time frequency specto-

grams. The current data show that there were differences in beta band envelope across the synchronise and syncopate conditions. This suggests that the beta band oscillations were partly dependent on incoming auditory stimulus and indicates that the pattern of beta band activity cannot be attributed to motor activity alone. The functional significance of this difference is discussed in greater detail in the following paragraph.

To the extent that beta band activity represented internal timing (Bartolo et al., 2014; Teki, 2014) it appears that syncopated tapping places more demand on systems governing internal timing as compared to synchronised tapping. One reason why the syncopate condition might require a greater degree of internalization is because the time at which to tap is not specified by an external cue. Instead, the external cue clearly marks the boundary of the time at which the participant should tap. The participant themselves must determine the precise moment at which to tap and this in turn places a greater demand on internal timing. This form of timing is not dissimilar to an fMRI study by Coull et al. (2013) in which a subject had to press a button after they felt a certain amount of time had elapsed (rather than being cued by an external stimuli as precisely when to press a button). Such an interpretation is also broadly consistent with functional neuroimaging data reporting that syncopation activates a much broader network of regions than synchronisation (Jantzen et al., 2004; Mayville et al., 2002) as it reveals that tapping between a beat places more demand on internal timing as compared to synchronisation. Additionally, early MEG studies showed that beta band power decreased more as the complexity of sequential movements increased (Manganotti et al., 1998), particularly when those movements were self paced (Kaiser et al., 2000). The observation of increased beta band activity

in the syncopation condition suggests it placed more demands on the motor system despite the fact that the overt movement requirements were the same.

Our findings appear to stand at odds with previous research. Fujioka et al. (2012) and Arnal et al. (2014) both reported that beta power is maximal prior to the occurrence of the sound so as to facilitate temporal processing. If indeed beta activity were only tracking the sound, then a different pattern of activity would have resulted. When epoched according to the onset of the response which occurs in phase with the sound (in the synchronise condition) or out of phase with the sound (in the syncopate condition), it would be expected that beta power peaks at different times in an out of phase relationship. As can be seen from our data, this did not occur (Figure 8.2). These apparent inconsistencies can easily be resolved by examining differences between methodologies. Previous research has (to the best of our knowledge), only documented beta band responses when listening to a passive sound or making some behavioural prediction. Unfortunately, this does not enable the separation of auditory activity from motor activity. By including the syncopate condition, I was able determine whether the beta band response was related to the sound or the tap. When a task does not require overt movement, the motor cortex is 'free' to track the sounds at the rate of stimulation and to generate efferent signals at that tempo (Arnal and Giraud, 2012). This also holds true for when a subject is asked to tap to a beat. However, when asked to tap between a beat, the beta band and the auditory and motor activity do not occur 'together', the auditory cortices seem to influence and predict motor activity rather than reflecting a response to the auditory stimulus per se.

Unexpectedly, no differences between synchronise and continue-nize conditions were found. This seems somewhat paradoxical given data from intracranial recordings suggesting the beta band is biased towards or attuned to the continuation phase of the task (Bartolo et al., 2014). The result could however be explained by the fact that participants were simply tapping rather than intentionally timing their response. If this were the case, then the beta band activity in these conditions could be significantly less than that which would be normally be associated with internal timing. Another possibility is that participants were imagining the sound in their head thereby minimising potential differences in beta band modulation. For this reason, I am hesitant to speculate about differences (or lack thereof) in beta envelope between the continuation and other experimental conditions. Consequently, the following discussion should be treated with a degree of caution.

When comparing the syncopate and the continue-pate conditions, a very different pattern of results was recorded compared to the synchronise continue-nize contrast. That is, beta synchronisation and desynchronisation was significantly greater for the syncopate compared to the continue-pate condition. At first glance, this result is somewhat perplexing given the former contains an external stimulus and the latter does not. When the timing cues are removed (continue-pate), it might be expected that an even greater demand is placed on structures and processes associated with internal timing. However, while continue-pate should indeed place some demand on internal timing because there is no external cue (in a similar manner as the continue-nize condition), it is much less demanding on internal timing precisely because that period of time in which to tap is not marked by an external stimulus.

The beta band signals observed in the time frequency spectrograms could have originated from a variety of sources. One possibility is that the signals are generated by the motor cortex. Alternatively, the beta band responses might actually be generated by the auditory cortex. It might also be the case that the signals are the result of an interaction of the auditory and motor cortices. Unfortunately, the analysis of spectotemporal data is not able to differentiate between competing explanations because they all produce similar results. Nevertheless, each explanation posits a different cause for the observed responses and can be represented by a different neural model. Accordingly, DCM is needed to assess how well each model explains the data in order to adjudicate between the competing explanations.

8.4.1 DCM comparing synchronise and Syncopate to Baseline

The directionality of the influence highlighted by the time frequency analysis is elucidated by winning models in the DCM analysis. The difference between the pacing conditions and rest was best explained by connectivity in the forward direction. This means that there was a unidirectional flow of information from the auditory to the motor cortex in both the synchronise and the syncopate conditions. This indicates, consistent with the time frequency analysis, that tapping to (or between) a beat relies on sound/auditory input and is largely underpinned by reliance on the auditory cortices. Indeed it is perfectly consistent with the idea that subjects use sensory feedback to judge whether they are keeping in time (Müller et al., 2000). On the one hand, this was not surprising given examining external pacing conditions were

being examined and it is reasonable to expect reliance on bottom up or sensory to motor connections.

On the other hand, since the DCM analysis was constrained to the beta band - thought to index internal timing and efference copies - the dominance of the forward (rather than backward) connections was somewhat puzzling. At a cursory glance, this seems run counter to the hypothesis that the beta band is not involved in sending efference copies to sensory regions of the brain (Arnal and Giraud, 2012; Arnal et al., 2014; Engel and Fries, 2010; Jenson et al., 2014a). However, closer inspection of the data reveals that such a conclusion would be unjustified. That the winning model contained models best explained the data simply implies the influence of the forward connections was greater than that of the backward connections. Importantly, it does not preclude the motor cortex sending efference signals to the auditory cortex via the beta band. This was further supported by the fact that in both baseline comparisons, that the backward connections explained the data significantly better than the null model. Nevertheless, it is important to consider the functional importance of the modulation in forward connections via the beta band.

Some insight into this can be gathered by examining a previous study. It has been reported that tactile stimulation of the lip or nose elicited beta rebound in the hand area of the motor cortex (Gaetz and Cheyne, 2006). The authors suggested that the beta band controls the ongoing coordination of sensory input and motor output maintained by continuous input from the periphery via somatosensory afferents. The results of the DCM analysis (and in particular the winning model containing forward connections) suggest that a similar process may be occurring during sensorimotor

synchronisation. In other words, the beta rebound might reflect the coordination of motor output by sensory (auditory) input and the auditory cortices may influence rhythmic motor output because they have the ability to process temporal regularities (Tecchio et al., 2000). These authors presented subjects with different trains of sounds containing varying degrees of isochrony. The inter-stimulus interval of the trains was varied by a perceptible (20%) or an imperceptible (2%) amount around a central value of 500ms. Tecchio et al. (2000) found that the amplitude of the M100 response increased as the interstimulus interval increased in not only the perceptible (20%) condition, but also in the imperceptible (2%) condition. Their findings were taken to suggest that the auditory cortex has the ability to process temporal regularities. The data from the present experiment support this contention and further suggest that the ability of the auditory cortex to process temporal regularities might extend to the temporal regularities of motor activity via the beta band. That is to say, during an active task, the auditory cortex (and perhaps any sensory region), might be able to predict motor activity. This prediction is not necessarily dependent on efference copies from the motor cortex, but is also not an independent process. Over time, the prediction of the motor activity by the beta band in the auditory cortex is updated according to the pattern of motor movement (efference copies from motor to auditory).

Alternatively, the presence of the forward connections could indicate the auditory cortex updates the motor cortex based on the pattern of movement relative to the sound. This proposal is in line with recent research showing that the characteristics of an auditory stimulus can influence isochronous movements and specifically those related to timing (Bravi et al., 2014). Their experiment provides evidence at

a behavioural level for how the properties of an auditory stimulus can influence the pattern of isochronously timed movements. By extension, the same process should be occurring at a neural level. The following implication is that the auditory cortex exerts some degree of causal influence over the motor cortex during isochronous movements perhaps via many different frequencies. However, since the target of the auditory cortex is the motor cortex, the influence is at least partly exerted across a frequency band known to be associated with motor activity. Given the role of the beta band in motor activity (Kilavik et al., 2013), the beta band seems like the perfect candidate through which the auditory cortex might influence the motor cortex. I demonstrate that the auditory cortex does indeed exert some degree of control over the motor cortex. This control is most evident in the synchronise condition in which an individual is attempting to entrain to a beat but perhaps also occurs in the syncopation condition. Recent work by Fujioka et al. (2013) seems to confirm this by showing that the contribution of auditory processing to rhythm processing depends on the timing and structure of movement. It should be emphasized that while the data suggests an influence of auditory regions over motor regions, that is not to this is the only region that is involved in timing (or that the motor cortex is uninvolved in such a process).

8.4.2 Comparison of synchronise and Syncopation

In addition to comparing synchronise and syncopate to baseline, both pacing conditions were also directly compared. When testing the between subjects effects, it was assumed that syncopation would require additional/stronger connections than

synchronisation. It was found that the difference between synchronise and syncopation was best explained by connections in the forward and backward directions. This suggests that in the beta band, syncopation requires stronger connections in the forward and backward connections. The fact that backward connections add a significant amount of explanatory power over and above forward connections alone, indicates syncopation is substantially more difficult than synchronisation and places a much greater demand on the systems governing external timing. This finding is in line with research showing the former condition recruits a much wider range of brain areas (Jantzen et al., 2004; Mayville et al., 2002). Given the beta band is thought to index internal timing (Bartolo et al., 2014; Teki, 2014), the influence of the backward connections suggests, in agreement with the time frequency results, that syncopation is also more demanding than synchronisation.

These results extend Witt and Stevens finding by showing that that the motor cortex exerts control over the auditory cortex specifically via the beta band (Engel and Fries, 2010; Wang, 2010; Arnal et al., 2011; Arnal and Giraud, 2012; Arnal et al., 2014). To the extent that the motor cortex sends a signal to the auditory cortex via the beta band around the time of movement and such signals can be called an 'efference copy', these findings suggest that the responses observed in the time frequency analysis may indeed be the efference copies hypothesized by Arnal and Giraud (2012). As such, this study demonstrates experimentally that the motor cortex actively constrains the auditory cortex via the beta band during two different forms of sensorimotor synchronisation (synchronise and syncopate). Notably, although the winning model in the synchronise condition did not contain backward connections, that does not preclude the generation of efference copies by the motor cortex. In-

deed in each condition, the backward model still explained a significant amount of variance over and above the null model.

8.5 Limitations and Conclusion

As a method DCM, is a powerful tool for determining causal influences that certain regions have over others. However, some authors offer caveats that it is difficult to determine if the winning model is truly the best or the closest to the truth (Lohmann et al., 2012). The present research was limited in scope because it only examined the role of the auditory and motor cortices in sensorimotor synchronisation using DCM in healthy adults. It is well established that the perception and production of rhythmic stimuli or movements involves a wide variety of frequencies (Bartolo et al., 2014; Cirelli et al., 2014; Fujioka et al., 2009, 2012; Zanto et al., 2006). That is to say, the induced responses are unlikely to be confined to the beta band. Future research may wish to investigate cross frequency coupling and how this might differ across synchronisation and syncopation. Given the pattern of results described here, it would be interesting to investigate whether similar responses can also be identified in individuals with stuttering and other disorders that are thought to involve aberrant interactions between the auditory and motor systems (Hickok et al., 2011). Additionally, it is noteworthy that a number of previous studies have documented a wide network of regions other than the auditory and motor cortex are active during synchronisation and syncopation. These include but are not limited to the basal ganglia, cerebellum, right inferior frontal gyrus, supplementary motor area, premotor cortex (Jantzen et al. 2004; Merchant et al. 2013; Wiener et al. 2010 and see for

review Pollok et al. 2006). Consequently, future research may wish to use DCM to examine the causal interactions of these regions and whether the addition of these regions improves the explanatory power of models containing the auditory and motor cortices alone. Finally, no attempt was made to control for differences in attention across the synchronisation and syncopation tapping. Given the stimuli were exactly the same, it was not expected that performing the each task would require different levels of attention. This is further supported by the lack of significant differences in the mean absolute deviation. Nevertheless, attention has been shown to influence beta band activity (e.g. Todorovic et al. (2015)) and future work should consider how this might influence neural activation in the context of paced finger tapping tasks. In summary, DCM was applied to the analysis of oscillatory responses of MEG data in the auditory and motor cortex. This study provides the first experimental evidence that the motor cortex actively constrains the activity of the auditory cortex during sensorimotor synchronisation, that the auditory cortex influences the motor cortex.

Chapter 9

Sensorimotor Synchronisation in Adults Who Stutter

9.1 Introduction

Stuttering is a disorder characterised by repetitions, prolongations and pauses that disrupt the flow of speech. The disorder generally appears in early childhood and affects about 5% of people (Månsson, 2000) though only 1% will continue to stutter into adulthood. Although stuttering manifests primarily in the domain of speech, there is also evidence to suggest that it affects other domains as well (e.g. Cross and Cooke, 1979; Hand and Haynes, 1983; Starkweather et al., 1984)

The cause of stuttering is not yet known, but is likely a combination of genes, linguistic factors and neural abnormalities (Packman, 2012). With respect to the neural underpinnings of stuttering, a number of theories have been proposed. These include (but are not limited to) alterations in hemispheric dominance

Behavioural studies show that adults who stutter (AWS) have increased temporal variability and longer reaction times for oral (Max and Yudman, 2003; Max et al., 2003) and non-oral movements (Hulstijn et al., 1992; Smits-Bandstra and Luc, 2007) relative to adults who do not stutter (AWDS). These results that suggest that stuttering is a motor control disorder not solely confined to the domain of vocalisation. In this regard, behavioural studies are also complimented by results from neurophysiological studies. For example, during speech, neural activation spreads from the mouth area of the motor cortex to the hand area of the motor cortex in AWS but not AWDS (Salmelin et al., 2000). AWS show abnormal excitability in both the tongue (Neef et al., 2011a, 2015b) and hand representation of the motor cortex (Alm et al., 2013; Busan et al., 2013), At the same time however, there is also evidence to suggest that AWS and AWDS do not differ in their ability to

produce rhythmic movements (e.g. Melvine et al., 1995; Max and Yudman, 2003; Zelaznik et al., 1994) raising doubts over claims that stuttering is a symptom of a more generalised motor disorder.

The fact that there are few differences in behavioural performance in tapping to a beat does not necessarily warrant the conclusion that AWS are unimpaired in their timing performance on simple tasks. The lack of between group differences between AWS and AWDS may partly be driven by the repetitive nature of tapping in time with a beat. Most studies investigating timing performance in AWS have done so using externally timed movements. Recent work with 100 healthy adults shows motor timing variability is significantly reduced when tapping in time with a metronome as compared to tapping without one. (Sundqvist et al. 2015, see also Hulstijn et al. 1992; Kleinow and Smith 2000; Smith and Kleinow 2000). Repetitive tapping tasks may simply not be demanding enough to elicit behavioural differences between AWS and AWDS. Increasing the difficulty associated with such tasks and thereby placing greater demands on systems governing timing may be able to elicit differences in behaviour between AWS and AWDS (Webster, 1989).

While overt behavioural performance of AWS and AWDS on tapping tasks may be the same, the underlying neural processes may be different. A recent study applied repetitive TMS to the left and right dorsal premotor cortex of AWS and AWDS during paced finger tapping (Neef et al., 2011b). Left handed tapping of AWDS was impaired by stimulation of the left dorsal premotor cortex but left handed tapping of AWS was impaired by stimulation of the right dorsal premotor cortex. This is particularly interesting in light of the fact that the right inferior frontal

gyrus is part of a core timing network (Wiener et al., 2011) and its relative activation is associated with decreased stuttering severity (see Belyk et al. 2015 for a meta analysis). The finding of Neef et al. (2011b) suggests that AWS might be using the right inferior frontal gyrus to compensate for timing deficits elsewhere in the brain. If such compensation is effective in ameliorating stuttering, neural compensation should minimise behavioural differences between AWS and AWDS. The possibility that neural compensation is masking behavioural differences has two major implications:1) In the absence of neural compensation there should be evidence of differences in behavioural performance between children who stutter (CWS) and children who do not stutter (CWDS) and 2) In the absence of behavioural differences, there may be evidence of differences in neural activity between AWS and AWDS. These implications make strong predictions about what to expect from behavioural and neuroimaging/neurophysiological data when testing AWS and CWS on timing tasks.

The first implication can be tested by comparing behavioural performance of children who do and do not stutter in the perception and production of rhythm. Because CWS have not stuttered for as long as AWS they much less likely to exhibit extensive compensatory neural reorganisation. In agreement with this idea, work by Chang and Zhu (2013) showed that CWS did not exhibit the increases in white matter in right frontal regions that has previously been seen in AWS. Interestingly though, a later study by the same group showed that AWS do exhibit increases in fractional anisotropy in the cerebellum (Chang et al., 2015) a region that has also been implicated in timing and prediction (see Ivry and Schlerf, 2008). Behaviourally, some CWS exhibit greater variability than CWDS when hand clap-

ping (Olander et al., 2010). The percentage of CWS showing greater variability than CWDS corresponds to the percentage of children whose stuttering persists into adulthood. As such, the authors suggested the degree of variability in hand clapping may predict whether or not a child recovers from stuttering (Olander et al., 2010). CWS also exhibit poorer behavioural performance than children who do not stutter (CWDS) on finger tapping tasks (Falk et al., 2014, 2015). Not only that, but recent work also shows that CWS exhibit deficits in the discrimination of different types of rhythm (Wieland et al., 2015). Although these studies did not record neuroimaging data, it is likely that the behavioural differences were also accompanied by corresponding differences in neural activity. Since CWS do not exhibit as extensive neural compensation as AWS (Chang and Zhu, 2013), any neural differences may be causally related to stuttering. However, it could be argued that the differences in behavioural performance would potentially confound the interpretation of any concurrently measured neural activity. Any apparent differences in neural activity thus measured might simply be the result of measuring brain activity at different points in the same neural processes, rather than because there are actually differences at the same point in the neural process.

If neural compensation is masking behavioural performance, there may be evidence of differences in neural activity on timing tasks between AWS and AWDS even in the absence of behavioural differences. Measuring neural activity in the absence of differences in behaviour makes it easier to interpret subsequent between group differences. Therefore when seeking to compare neural activity between AWS and AWDS it would be sensible to use a task in which there are not likely to be any behavioural differences. A number of previous investigations have found no

differences in accuracy or variability when synchronising oral or non oral motor movements to auditory tones (Hulstijn et al., 1992; Max and Yudman, 2003). These tasks (or some variation thereof) would be ideal to study differences in neural activity between AWS and AWDS.

The perception and production of isochronous intervals is associated with specific patterns of neural activity. Most studies investigating brain activity during synchronisation (tapping with the beat) and/or syncopation tapping (tapping between the beat) have done so using fMRI. Early research by Rao et al. (1997) showed that tapping in time with a metronome activated the SMA and auditory regions. Lewis et al. (2004) found that as the complexity of tapping increased (as measured by a greater number of, and variation in, temporal intervals), that there was greater demand on the right dorsolateral prefrontal cortex as evidenced by an increase in BOLD response. In the same year, Jäncke et al. (2004) examined the preceding effect of synchronised and syncopated pacing on a subsequent period of rhythmic tapping where the pacing beat had been removed. They found that syncopated tapping activated a more distributed network of regions than synchronised tapping, suggesting that it placed more demands on the systems governing timing. Interestingly, they also found that the tapping without a pacing beat was influenced by the type of paced tapping (synchronised or syncopated) that preceded it. These results were largely confirmed by Mayville et al. (2002) who found that syncopated finger tapping elicited greater activation in the basal ganglia and cerebellum than did synchronised tapping, suggesting that the former condition was significantly more demanding on internal timing systems than the latter.

Two recent meta-analyses of speech show that stuttering is associated with overactivation of the supplementary motor area and the right inferior frontal gyrus (Belyk et al., 2015; Budde et al., 2014), regions which are both part of a core timing network and are engaged in a variety of timing tasks (Wiener et al., 2011). Additionally, people who stutter show structural (Chang and Zhu, 2013) and functional (Lu et al., 2010b,a) abnormalities in the basal ganglia. This region of the brain responds to temporally regular beats (Grahn et al., 2007) and is involved in the initiation, execution and sequencing of speech movements (Civier et al., 2013; Price, 2010; Jin and Costa, 2015). A regular metronome raises the level of activity in the basal ganglia of AWS to the level of AWDS during speech (Toyomura et al. 2011 see also Toyomura et al. 2015). Thus many of the areas found to exhibit functional abnormalities during paced finger-tapping exhibit abnormalities in stuttering.

Notably, most imaging experiments on finger tapping (paced or unpaced) have been conducted using fMRI or PET (see for review Chauvigné et al., 2014; Witt et al., 2008). While fMRI and PET both have excellent spatial resolution, they have poor temporal resolution compared to MEG and EEG. When studying neural responses to timed and rhythmic movements, it is not only important to identify which areas are involved in producing rhythmic movements, but also how the neural representation of such behaviours evolves over time. Neural responses to finger tapping are evident not only in haemodynamic response and evoked responses, but also in the induced oscillatory response. This oscillatory response occurs over a hundreds of milliseconds, much faster than the haemodynamic response. Neural oscillations are usually thought to be involved in short or long range communication between areas of the brain (Thut et al., 2012). Gerloff et al. (1998) used EEG to show

that internally paced finger tapping was associated with more coherence - or coupling - between the premotor cortex and the SMA in the beta band. Similarly, Manganotti et al. (1998) showed that the decrease in power and an increase in coherence in the beta band was greater for more complex movements as opposed to simple ones. Notably, Mayville et al. (2001) used MEG to examine oscillatory activity in the beta band during synchronised and syncopated finger tapping. These authors found that oscillatory beta band power was significantly greater during syncopated tapping than during synchronised tapping, a finding thought to index task difficulty. Jantzen et al. (2001) also found that practise leads to a reduction in the differences in oscillatory activity between synchronisation and syncopation.

The main reason studies such as (Gerloff et al., 1998; Jantzen et al., 2001; Mayville et al., 2002) focus on the on the beta band (13-30Hz) because this frequency is traditionally associated with movement. It is well established for example that imagining, observing or executing a movement leads to a decrease in beta band power that persists until the movement stops (Burianová et al. 2014, see for review Kilavik et al. 2013). Recent work however links the beta band with temporal processing (see for review Arnal and Giraud, 2012; Merchant et al., 2015). The perception of isochronous sounds modulates the envelope of oscillatory beta activity such that it peaks at the time when the sound is expected (Cirelli et al., 2014; Fujioka et al., 2012). These authors suggested that the beta oscillatory envelope may represent the internalization of a temporal interval. In line with this reasoning, Kononowicz and van Rijn (2015) showed that larger beta amplitudes are associated with longer estimations of time. Interestingly, the level of beta band activity is correlated with synchronisation accuracy (Pollok et al., 2009). Some authors have (Bartolo et al.,

2014; Merchant et al., 2015) demonstrated that where the demands on an internal representation of time are greater (i.e. during internally rather than externally paced finger tapping), there is enhanced beta band activity in the putamen (see also Bartolo and Merchant, 2015).

The association between beta band activity and the activation of the putamen is particularly interesting given the putative involvement of that structure in the aetiology of stuttering (Alm 2004; Chang and Zhu 2013; Civier et al. 2013; Ingham et al. 2013; Toyomura and Omori 2004; Toyomura et al. 2011, 2015 and for a discussion on the links between beta band and stuttering see Etchell et al. 2014b). Although it is not usually viable to make invasive recordings from subcortical structures in humans, it is nevertheless possible to record beta band activity from regions overlying the cortex. Most notably, beta oscillations during perception of rhythm have been measured from the auditory and motor cortices (Fujioka et al., 2012). Neural oscillations in the beta band may not simply reflect motor activity per se, but also the effect of timing on motor movements. To the best of our knowledge, no study has compared the beta band activity (or for that matter any kind of neural activity) in AWS and AWDS during the production of rhythmic finger sequences

The present study sought to address this gap in the literature by recording neuromagnetic beta band activity from AWS and AWDS during a simple (synchronisation) and more complex (syncopation) paced and finger tapping task. Because meta analyses of paced tapping tasks reported activation in auditory and motor areas (Chauvigné et al., 2014; Witt et al., 2008), I opted to measure beta band activity from these three regions. Given the association with the basal ganglia and the

beta band in internal timing (and syncopated tapping) as well as the basal ganglia in stuttering, three hypotheses were formed. This entailed the expectation that 1) there would be no difference in behavioural performance between AWS and AWDS on the synchronisation condition but there would be differences in behaviour on the syncopation condition. Additionally, that 2) beta band modulation would be greater for syncopation than for synchronisation in the motor cortex in both AWS and AWDS. Furthermore, it was anticipated that 3) AWS would exhibit greater beta band activity than AWDS on the more demanding syncopation task but not the less demanding synchronisation task in the motor cortex.

9.2 Method

9.2.1 Participants

Participants were 11 male and 3 female AWS aged between 20 and 81 years, (M=49, SD=19 years) and sex matched AWDS aged between 20 and 80 years, (M=49, SD=20 years). In each group (AWS and AWDS), 12 participants were right handed and 2 participants were left-handed. Table 9.1 summarises the demographic characteristics of the AWS including self-reported measures of stuttering severity. AWS were previously diagnosed as stutterers by a speech pathologist. Other than stuttering, AWS (and AWDS) did not report having any other neurological disorder. Participants gave written informed consent before the start of the experiment and were given cash payment in return for their time. This study was approved by the Macquarie University Ethics Committee (see Appendix E for final approval).

Table 9.1: Demographic Characteristics of Adults Who Stutter. The percentage of stuttered syllables is derived from the percentage of syllables stuttered during a ten minute voice sample. The Usual stuttering severity (and range) refers to the self reported stuttering severity from 1 to 10 where 1 is no stuttering at all and 10 is the worst stuttering imaginable. The Therapy column indicates whether the participant had treatment as a child and/or an adult

ID	Age	Sex	Handedness	% Syllables Stuttered	Usual Stuttering Severity (Range)	Age of Onset	Therapy height
S1	20	F	RH	4.2%	4 (2-9)	4.5	Child/Adult
S2	23	M	RH	1.4%	3.5 (2-6)	1.5	Child
S3	23	M	RH	2.7%	4.5 (1-10)	4.5	Child/Adult
S4	29	M	RH	0.5%	2 (2-4)	9	Child/Adult
S5	29	M	RH	2.6%	3 (2-4)	5	Child
S6	46	M	RH	2.6%	2.5 (1-7)	6	Child
S7	51	M	LH	0.6%	2 (2-2)	2.5	Child/Adult
S8	53	M	RH	0.5%	2 (2-7)	7	Adult
S9	61	M	LH	0.2%	2.5 (1-10)	4.5	Child/Adult
S10	62	M	RH	4.4%	5 (3-9)	2	Adult
S11	64	M	RH	3.0%	3 (1-7)	7	Child/Adult
S12	64	F	RH	0.9%	2 (2-4)	5	Child/Adult
S13	67	F	RH	3.4%	4 (2-5)	3	Child/Adult
S14	81	M	RH	2.4%	2 (2-7)	6	Child/Adult

9.2.2 Behavioural Task

The paradigm used here is identical to the one described in Chapter 8. Participants were required to tap in time with the beat (synchronise) or between the beat (syncopation) and to continue tapping once the beat had been stopped. Participants responded by tapping their right index finger on a pneumatic tapping pad ($http://www.curdes.com/hhsc-1x1-tp.html$). They were required to tap in such a way that their finger came into contact with the tapping pad at the same time as the sound (synchronisation), when the sound would have occurred (continue-nize) or to tap between the sounds (syncopation) or between when the sounds would have occurred (continue-pate). These instructions were given the participant before entering the MEG and once again directly before the start of the experiment.

A visual cue lasting for (1000ms) indicated whether the subject was required to perform synchronisation or syncopation tapping. A fixation cross was presented throughout the tapping phases. For each form of pacing, 24 sounds were presented with an onset asynchrony of 800ms (a stimulus rate of 2.5Hz). Sounds were presented through a speaker (Panphonics) located at the feet of the participant and played at 75dB sound pressure level (as measured from the head position inside the dewar). After every 24 paced and 24 unpaced taps (one trial) a 1000Hz sound was played for 1000ms signalling the participant to stop tapping. The next trial began after 1000ms. After one synchronise and one syncopate trial, participants were able to rest for a period of 15-20s before the beginning of the next tapping trial. All stimulus

sequences were presented on a Dell Pentium 4 computer running Windows 7 using Presentation 16.3 (Presentation Neurobehavioral Systems, Albany USA).

Here only the data from the synchronise and syncopate conditions are reported. Accuracy and variability of tapping were recorded by measuring the tap to tone asynchrony and the mean absolute deviation (MAD) of the tap to tone asynchrony. The reasoning behind using this measure (MAD) is illustrated in the following example. If in the synchronisation condition, a participant taps 100ms before the tone and 100ms after the tone, the mean asynchrony would be zero. The mean absolute deviation would be 100ms. The MAD is therefore more sensitive than the mean asynchrony because it can account for asynchronies in the positive and the negative direction.

9.2.3 MEG Recording

Neuromagnetic responses were recorded using a magnetoencephalograph consisting of 160 coaxial first order gradiometers (Model PQ160R-N2, KIT, Kanazawa, Japan). Prior to MEG measurements, five marker coils were placed on an elasticized cap on the participant's head and their positions and the participant's head shape were measured with a pen digitizer (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing marker coils in the MEG dewar both before and after the recording session. Participants head movement did not exceeded an average movement threshold of 5 mm. During recording, the participants lay supine with their arms by their side.

9.2.4 Data Analysis

Data were analysed using SPM12 (Wellcome Institute, London, UK) running on Matlab R2014a (The MathsWorks, Natrick, USA). The raw data was sampled at a continuous rate of 1000Hz. Once it had been collected, the data was down-sampled to 250Hz, resulting in a temporal resolution of 4ms. This signal was then band-pass filtered from 1 to 40Hz. The MEG epoch extracted for analysis was 700ms before and after the onset of the response and the onset of the sound for the synchronize and the syncopate conditions. The SPM12 fieldtrip visual artefact rejection function was then used to remove all trials containing amplitudes that had Z values of greater than 2. Using this method, less than 5% of trials were excluded for each condition. Based on the unaveraged evoked data, a linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997) was used as a spatial filter to estimate the source time series.

9.2.5 Evoked Data

Unless stated otherwise, all analysis is conducted in source space. A linearly constrained minimum variance (LCMV) beamforming was used to extract sources from the auditory and motor cortices based on a priori coordinates from previous literature. Specifically, the MNI coordinates of the left and right auditory sources were [-47,22,11 and [53,-21,15] taken from Jantzen et al. (2004). The coordinates for the left motor cortex (i.e. contralateral to the tapping hand) were [-36,-21,54] and were taken from Witt et al. (2008). Zero-phase root mean square (RMS) smoothing (an RMS average of activity in a moving window of 5 samples with a consecutive overlap

of 4 samples) was applied to the three sources in order to remove the effects of waveform polarity that could differ between subjects. The evoked analysis was conducted for the purpose of testing whether any low-level auditory processing differences existed between AWS and AWDS. All statistical testing of virtual sensor data was performed using non-parametric point-by-point comparisons via the non-parametric permutation statistics implemented in the $std_s tat$ function of EEGLAB (Delorme et al., 2006). All tests are corrected using the false discovery rate (FDR; Benjamini and Yekutieli 2001) approach unless otherwise specified. Independent sample t-tests to compared the amplitude of the RMS evoked responses between AWS and AWDS for the synchronise and syncopate conditions. Additionally, paired t-tests were used to compare the amplitude of the RMS evoked responses for the synchronise and syncopate conditions within the AWS and AWDS groups separately. The statistical tests were implemented in the 'std_stat' function of the EEGLAB toolbox (Delorme et al., 2006) and were corrected for multiple comparisons using a false discovery rate (FDR) of $p<0.05$.

9.2.6 Time Frequency Data

Time-frequency decompositions of the virtual sensor time-series were calculated separately for each individual, location and stimulus condition from 1-40Hz using a Morlet wavelet transform (Bertrand et al., 1994) and averaged across trials. The averaged data were then cropped in the time domain from -500 to -500ms so as to reduce artefacts occurring at the edge of the spectrogram. This epoch was chosen because it was sufficient to visualise a full cycle of taps and tones. Once the data

had been cropped, the power was rescaled at each time point to the mean frequency power across the entire epoch. For statistical analysis, modulation was averaged over the canonical beta range of 13-30Hz. Induced time frequency data was statistically analysed in the same way as the evoked data by using independent sample t-tests to compare beta modulation between AWS and AWDS for the synchronise and syncopate conditions. Paired t-tests were used to compare beta modulation between the synchronise and syncopate conditions within the AWS and AWDS groups separately. Both independent and paired t-tests were implemented in the std_stat function of the EEGLAB toolbox (Delorme et al., 2006) and were corrected for multiple comparisons using a false discovery rate (FDR) $p<0.05$.

9.3 Results

9.3.1 Behavioural Data

There was no significant difference between the mean asynchrony for the AWS (M = -33ms SD 32ms) and the AWDS (M = -15ms, SD 91ms) in the synchronise condition ($p<0.4887$, t = -0.704). Likewise, there was also no significant difference between the mean asynchrony for AWS (M = 7ms SD = 92ms) and AWDS (M=-30ms SD = 93ms) for the syncopate condition ($p<0.303$, t = -1.05). There was no significant difference between the MAD for the AWS (M=34ms, SD= 9ms) and the AWDS (M=33ms, SD=10ms) for the synchronise condition ($p<0.892$, t=-0.138). There was also no significant difference between the MAD for the AWS (M=66ms, SD=49ms) and the AWDS (M=40ms, SD=37ms) in the syncopate condition ($p<0.132$, t=-1.56).

9.3.2 Evoked Data

The evoked fields for the auditory and motor cortices were averaged relative to the time of the sound and the tap respectively and can be seen in Figures 9.1-9.3. There were no significant differences between AWS and AWDS in evoked activity in either the left or right auditory cortex for either the synchronise or syncopate conditions (see Figures 9.1-9.2 left column). There were also no significant differences between the synchronise or the syncopate conditions within either AWS or the AWDS (see Figures 9.1-9.2 right column).

Similarly, there were also no significant differences between AWS and AWDS in evoked activity in the left motor cortex for either the synchronise or the syncopate condition. (see Figure 9.3 left column). There were no significant differences between conditions for the AWDS group or the AWS group (Figure 9.3).

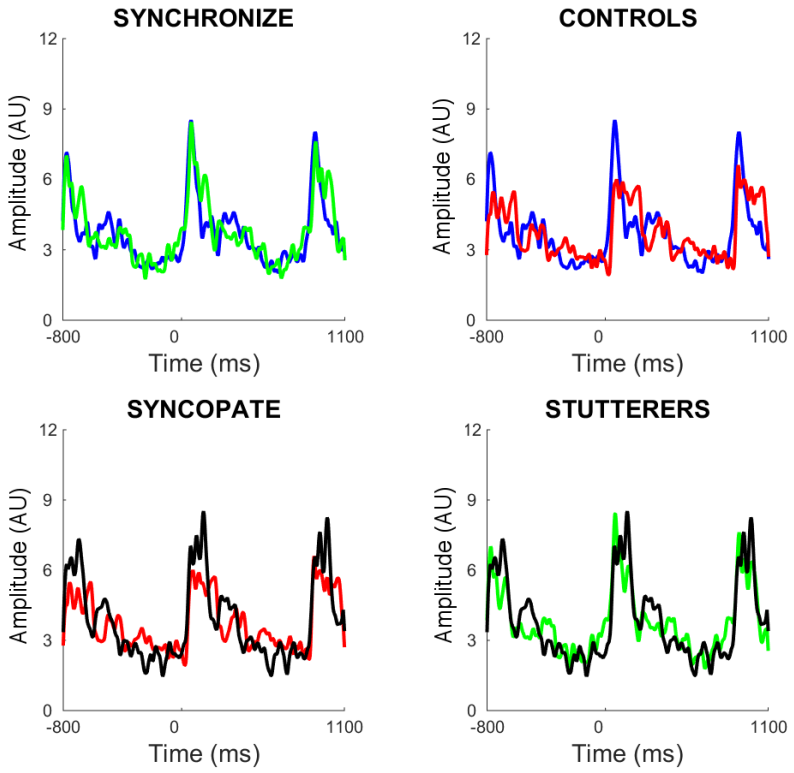

Figure 9.1: Grand mean of the RMS evoked responses in the left auditory cortex relative to the onset of the sound. The first two plots in each row/column show -800ms before and 1100ms after the onset of the tone. The green line and blue lines respectively depict the evoked response for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the evoked response for the AWS and the AWDS to the syncopate condition. The left column shows between group comparisons and the right column shows within group comparisons N=14

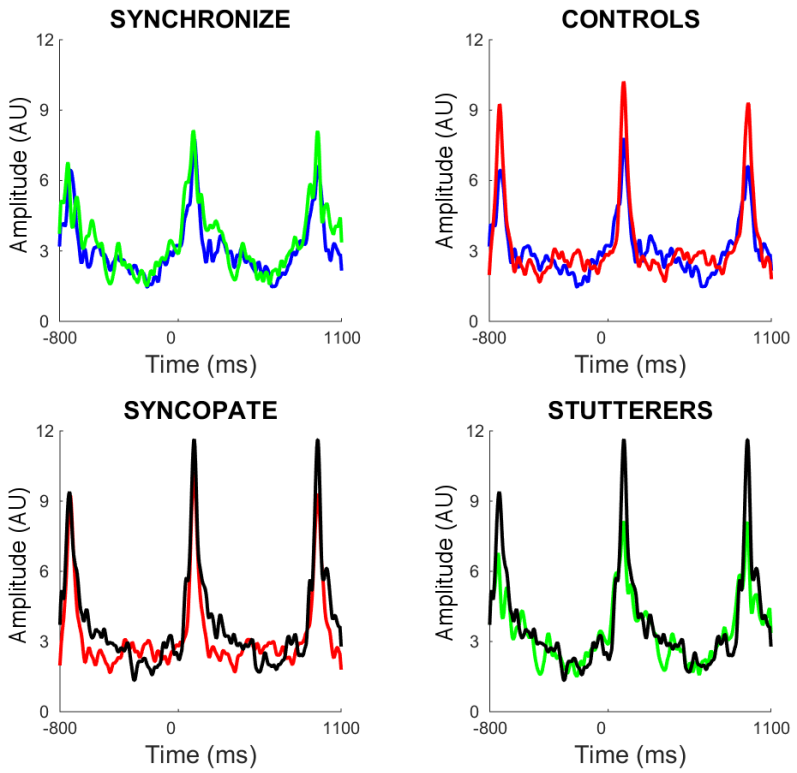

Figure 9.2: Grand mean of the RMS evoked responses in the right auditory cortex relative to the onset of the sound. The first two plots in each row/column show -800ms before and 1100ms after the onset of the tone. The green line and blue lines respectively depict the evoked response for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the evoked response for the AWS and the AWDS to the syncopate condition. The left column shows between group comparisons and the right column shows within group comparisons N=14

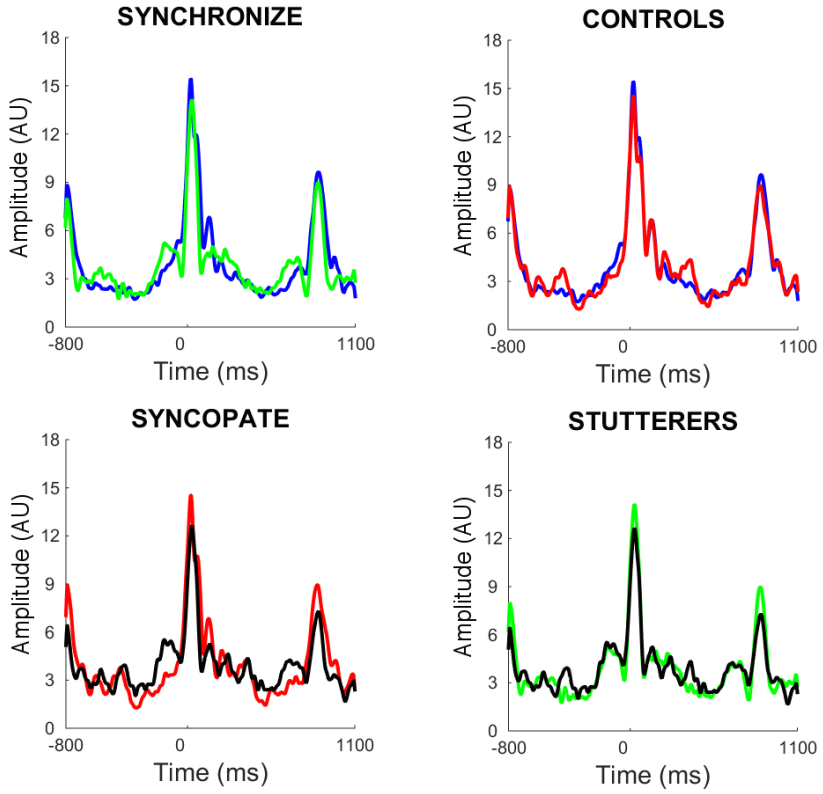

Figure 9.3: Grand mean of the evoked responses in the left motor cortex relative to the onset of the tap. The first two plots in each row/column show -800ms before and 1100ms after the onset of the tap. The green line and blue lines respectively depict the evoked response for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the evoked response for the AWS and the AWDS to the syncopate condition. The left column shows between group comparisons and the right column shows within group comparisons. The dark grey represents significant differences between conditions at an FDR corrected threshold of $p<0.05$. N=14

9.3.3 Time Frequency Data

The time frequency data for the 13-30Hz range can be seen in Figure 9.4-9.7. Note the out of phase beta modulation in the motor cortex during the synchronise and syncopate conditions when locked to the sound (Figure 9.7). Because motor responses in the synchronise and syncopate conditions occur either on or off the beat respectively, this is further confirmation that participants performed the task correctly and also that the extracted source is related to motor activity.

Non parametric t tests revealed no significant differences between AWS and AWDS in beta band modulation in the left and right auditory cortices (see Figures 9.8 and 9.9). Notably, in the left auditory cortex, there were significant differences between synchronise and syncopate conditions for both AWS and AWDS when locked to the onset of the sound (see Figures 9.8. In the right hemisphere, the AWDS but not the AWS showed differences between the synchronise and syncopate conditions. Figure 9.10 depicts the beta modulation between AWS and AWDS in the motor cortex when locked to the onset of the sound. Note there is no difference between AWS and AWDS, but that there is a difference between synchronisation and syncopation for both AWS and AWDS. Finally, there were significant differences between AWS and AWDS in the beta band in the synchronisation condition in the motor cortex when locked to the onset of the response. Specifically, AWS had more beta band modulation than AWDS in the left motor cortex (see Figure 9.11). Interestingly, there was no significant difference between AWS and AWDS in the syncopate condition (Figure 9.11). The dark grey represents significant differences between conditions at an FDR corrected threshold of $p<0.05$.

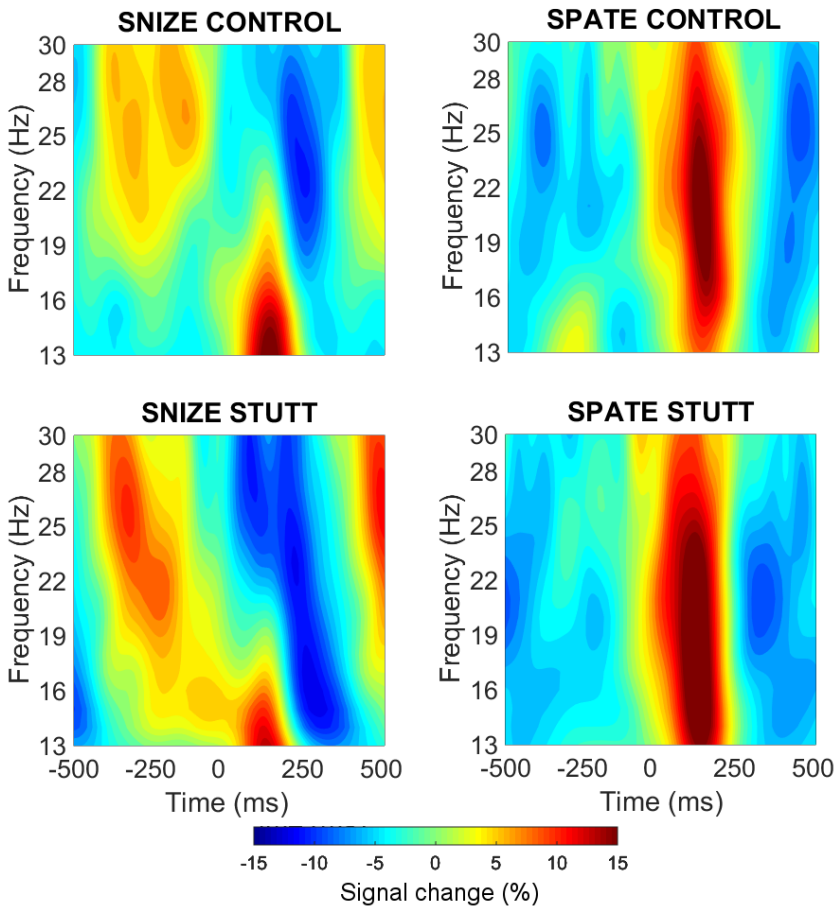

Figure 9.4: Grand mean time frequency plot for the left auditory cortex relative to the onset of the tone. The first two plots in each row/column show -500ms before and 500ms after response onset between 13 and 30Hz for each of the pacing conditions. The top and bottom rows depict the time frequency response for the synchronise and the syncopate conditions for the AWDS and the AWS respectively. N=14

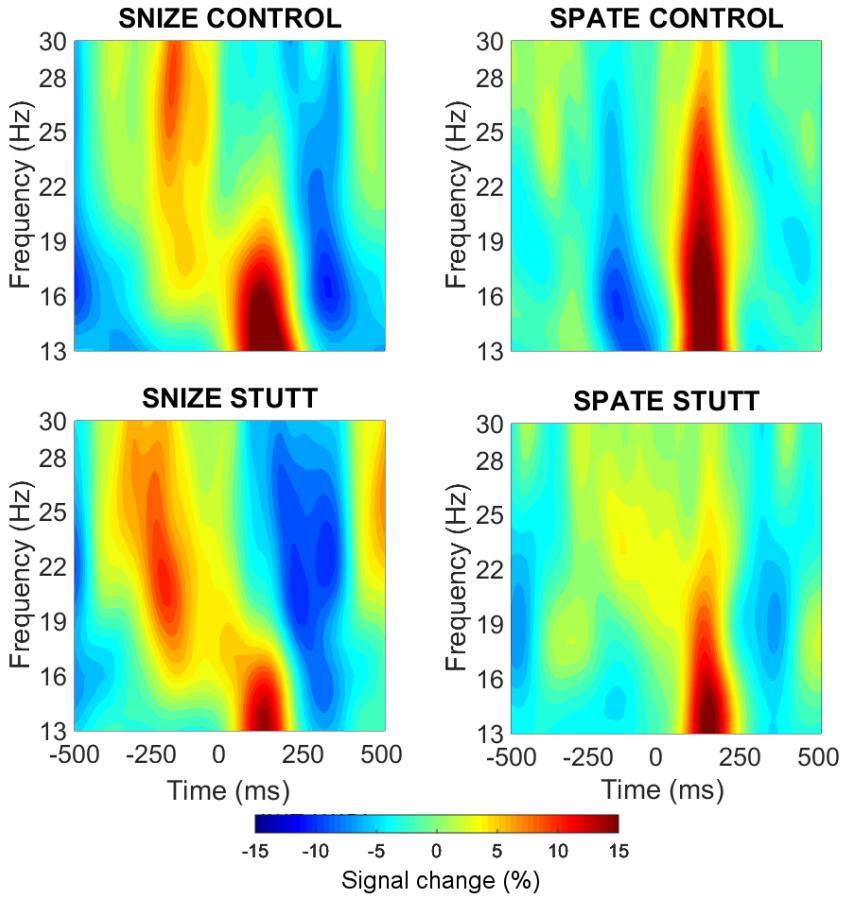

Figure 9.5: Grand mean time frequency plot for the right auditory cortex relative to the onset of the tone. The first two plots in each row/column show -500ms before and 500ms after response onset between 13 and 30Hz for each of the pacing conditions. The top and bottom rows depict the time frequency response for the synchronise and the syncopate conditions for the AWDS and the AWS respectively. N=14

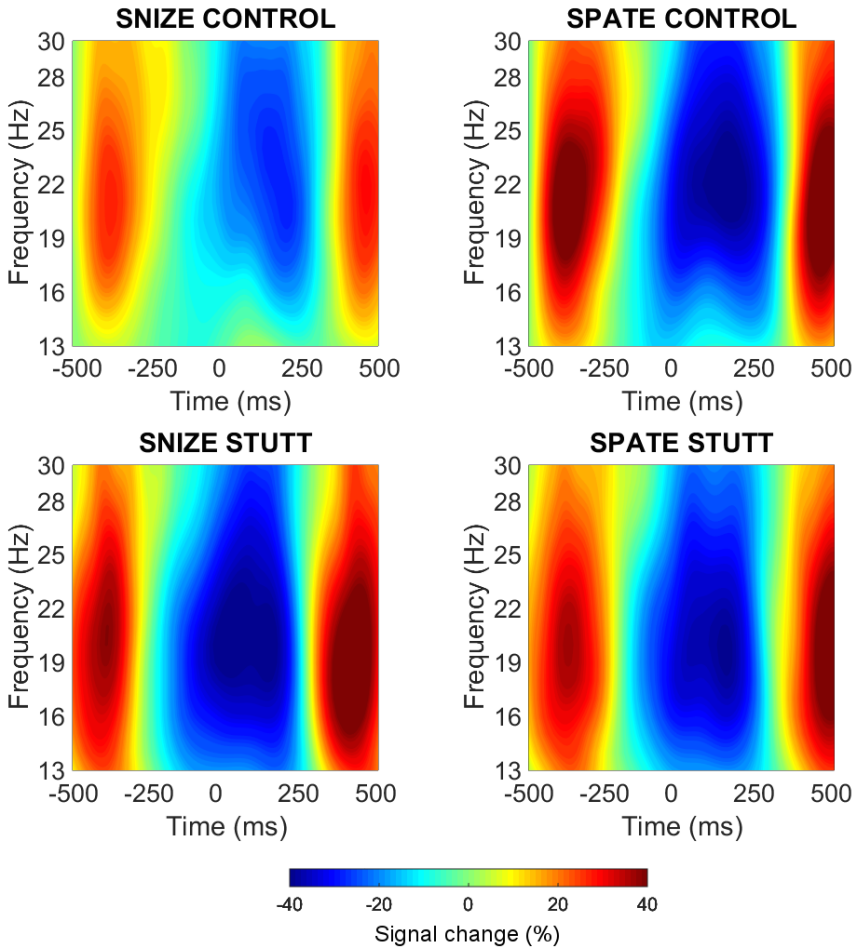

Figure 9.6: Grand mean time frequency plot for the left motor cortex relative to the onset of the tap. The first two plots in each row/column show -500ms before and 500ms after tap onset between 13 and 30Hz for each of the pacing conditions. The top and bottom rows depict the time frequency response for the synchronise and the syncopate conditions for the AWDS and the AWS respectively. N=14

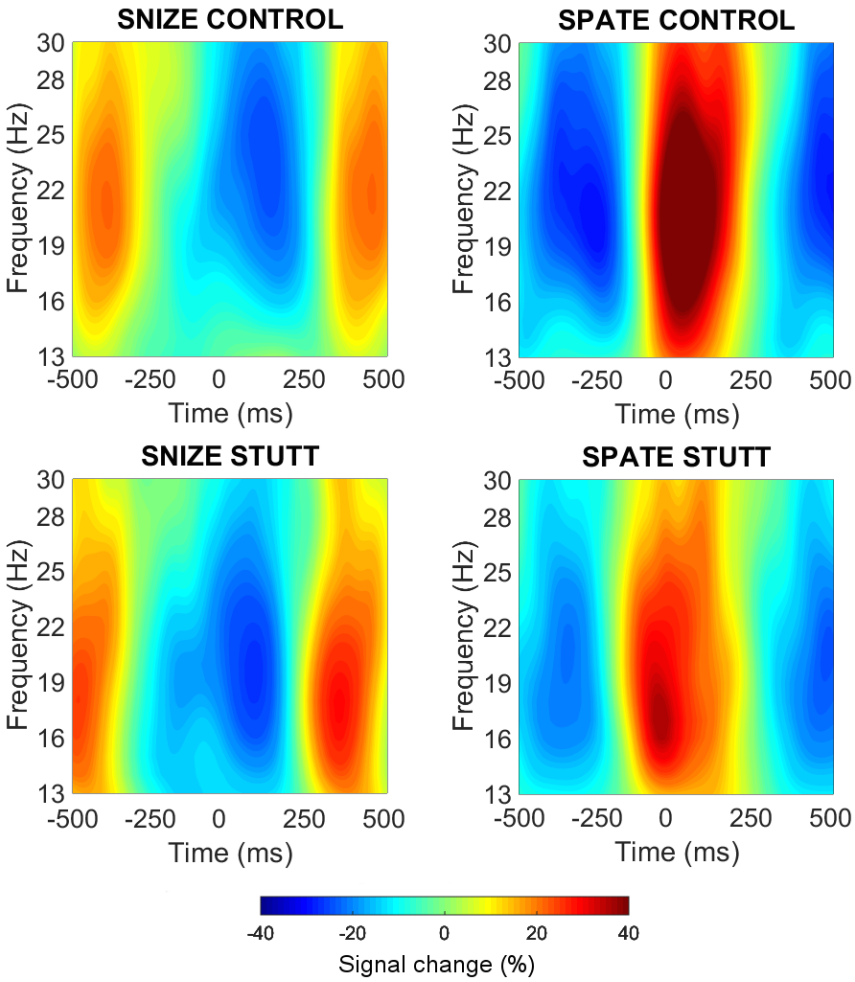

Figure 9.7: Grand mean time frequency plot for the left motor cortex relative to the onset of the sound. The first two plots in each row/column show -500ms before and 500ms after sound onset between 13 and 30Hz for each of the pacing conditions. The top and bottom rows depict the time frequency response for the synchronise and the syncopate conditions for the AWDS and the AWS respectively. N=14

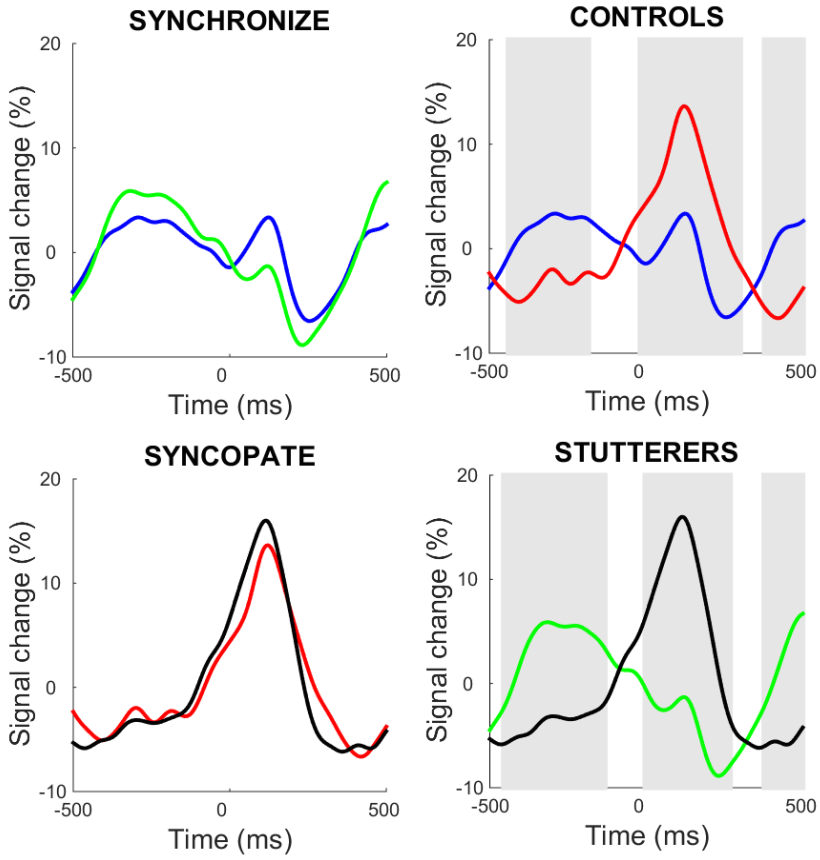

Figure 9.8: Grand mean of the time frequency response for the left auditory cortex collapsed across 13-30Hz for the relative to the onset of the tone. The first two plots in each row/column show -500ms before and 500ms after tone onset between 13 and 30Hz for each of the pacing conditions. The green line and blue lines respectively depict the beta modulation for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the beta modulation for the AWS and the AWDS to the syncopate condition. The left column shows between group differences and the right column shows within group differences

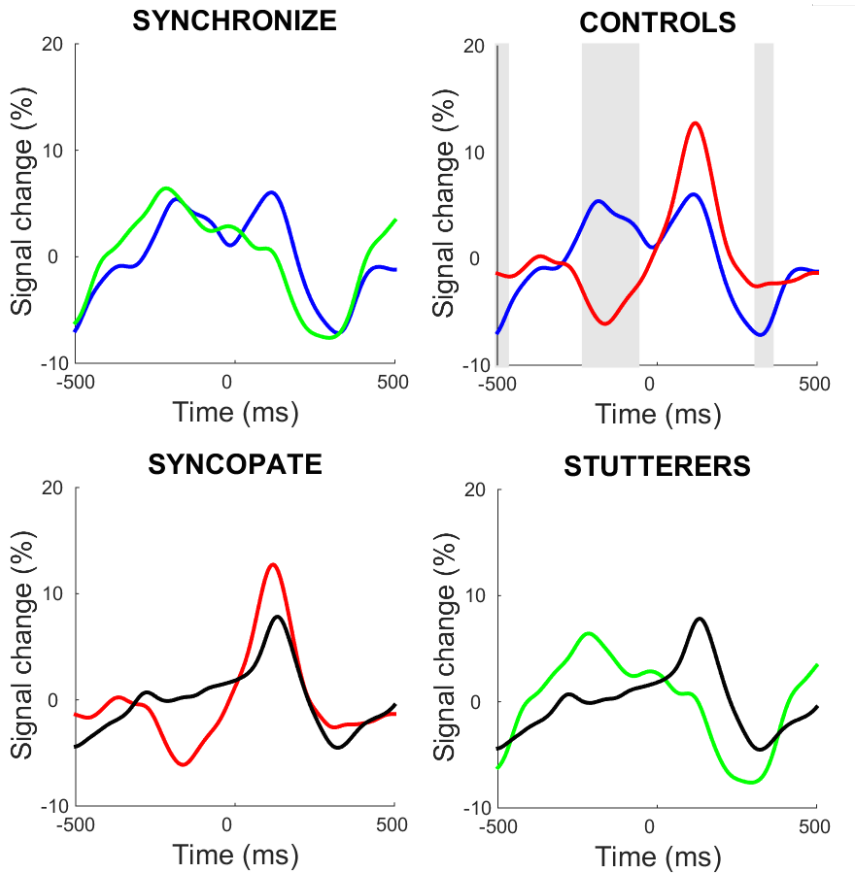

Figure 9.9: Grand mean of the time frequency response for the right auditory cortex collapsed across 13-30Hz for the relative to the onset of the tone. The first two plots in each row/column show -500ms before and 500ms after tone onset between 13 and 30Hz for each of the pacing conditions. The green line and blue lines respectively depict the beta modulation for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the beta modulation for the AWS and the AWDS to the syncopate condition. The left column shows between group differences and the right column shows within group differences

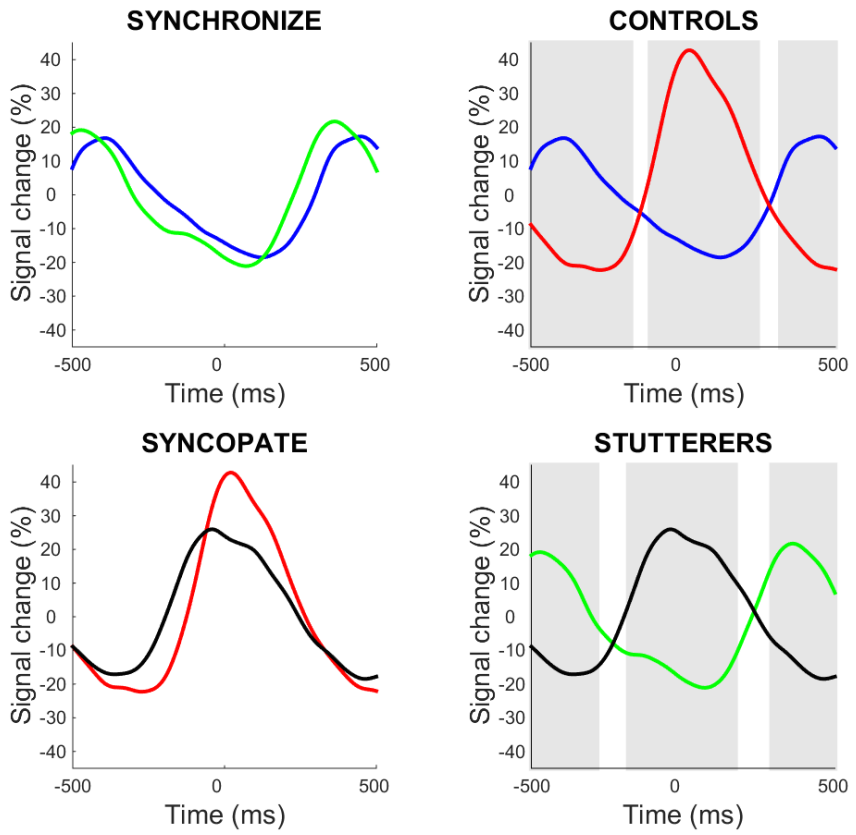

Figure 9.10: Grand mean of the time frequency response for the left motor cortex collapsed across 13-30Hz for the relative to the onset of the sound. The first two plots in each row/column show -500ms before and 500ms after sound onset between 13 and 30Hz for each of the pacing conditions. The green line and blue lines respectively depict the beta modulation for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the beta modulation for the AWS and the AWDS to the syncopate condition. The left column shows between group differences and the right column shows within group differences

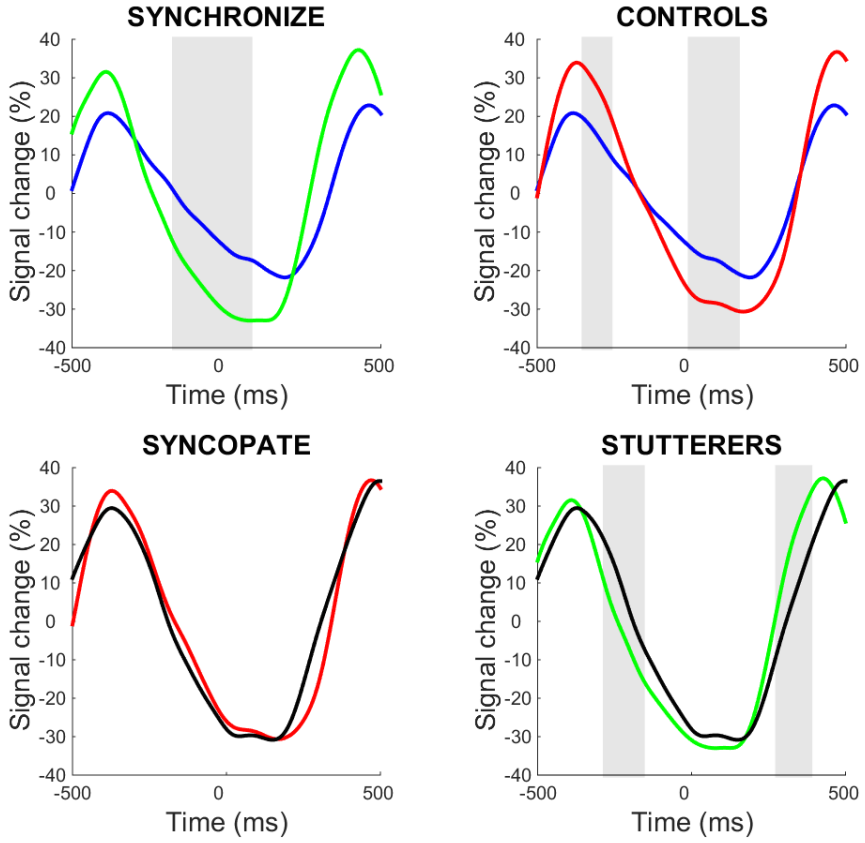

Figure 9.11: Grand mean of the time frequency response for the left motor cortex collapsed across 13-30Hz for the relative to the onset of the tap. The first two plots in each row/column show -500ms before and 500ms after response onset between 13 and 30Hz for each of the pacing conditions. The green line and blue lines respectively depict the beta modulation for the AWS and the AWDS to the synchronise condition. Similarly, the black and red lines respectively depict the beta modulation for the AWS and the AWDS to the syncopate condition. The left column shows between group differences and the right column shows within group differences

9.4 Discussion

The present study compared neuromagnetic beta band activity in AWS and AWDS during synchronisation and syncopation tapping. It was expected that AWS and AWDS would differ in behavioural performance on the syncopation but not the synchronisation task. Additionally, it was hypothesized that syncopation tapping would elicit greater beta band modulation than the synchronisation task in both AWS and

AWDS due to the former task placing more demands on internal timing. Furthermore, AWS and AWDS was expected to exhibit the greatest differences in beta band activity when performing the more demanding syncopation task, as compared to the synchronisation task.

The results of the experiment partially confirmed our first second and third hypotheses. Firstly, AWS and AWDS did not differ in variability on the synchronisation task. However, the groups also showed no difference in performance on the syncopation task. Secondly, AWDS but not AWS showed larger beta band oscillations in the syncopation compared to the synchronisation condition. Thirdly, this study found no differences in beta band oscillations between AWS and AWDS in the syncopation task. Instead it was only found between group differences in the synchronisation task. This study demonstrates for the first time that AWS differ from AWDS in beta envelope neural dynamics during simple paced finger tapping. The significance of these findings is discussed below.

9.4.1 Behavioural performance

The asynchronies and the mean absolute deviations of the tap were similar to previous reports of synchronised and syncopated tapping (e.g. Mayville et al., 2001; Pollok et al., 2009). There was no significant difference between groups for the synchronise condition. This was not unexpected and the lack of differences in overt behavioural performance between AWS and AWDS is broadly consistent with several studies that found no behavioural differences between groups (e.g. Max et al., 2004; Neef et al., 2011a). Importantly, the fact that there were no differences in behavioural perfor-

mance between AWS and AWDS during the synchronisation task perhaps suggests that group differences in beta band power are unlikely to be driven solely by differences in overt behavioural performance. There was also no difference in behavioural measures between AWS and AWDS in the syncopation task.

9.4.2 Evoked Data

Both AWS and AWDS show clear evidence of an evoked response to the stimuli in the auditory cortices (see Figure 9.2-9.3). Importantly, there were no differences between AWS and AWDS in the evoked response in either the left or right auditory cortex. This reduces the likelihood that differences between AWS and AWDS in the beta oscillations of the motor cortex (see below) are the result of low level auditory processing deficits. Similarly, there were no differences between AWS and AWDS in the evoked response in the left motor cortex.

9.4.3 Time Frequency Data

It is important to establish that the changes in beta oscillations were observed were attributable to the tap. If the pattern of activity in the motor cortex is a response to the sound, then there should be a similar level of beta band modulation between the synchronise and syncopate conditions when locked to the onset of the sound. This was not the case. Both the time frequency spectograms (see Figure 9.4) and collapsed beta band oscillations (Figure 9.7) showed that the peaks and troughs of beta band activity occurred at very different times. This out of phase relationship is precisely what would be expected if indeed the beta band reflected motor activity instead of

a response to the onset of the sound. This is because motor movements occurred at the same time as the sound in the synchronise condition but out of phase with the sound in the syncopate condition. Importantly, this out of phase relationship was seen for both AWS and AWDS.

The assertion that beta band oscillations are a reflection of motor activity was further confirmed by examining the neural responses locked to the onset of the tap. If beta band oscillations are associated with the tap, then there should be a similar pattern of beta band activity across the synchronise and syncopate conditions. Indeed both AWS and AWDS showed peaks and troughs of beta activity at the same time in the synchronise and syncopate conditions in the motor cortex (see Figure 9.4 and Figure 9.5).

9.4.4 AWDS Within Group Differences

As expected AWDS showed greater beta band activity during syncopation tapping as compared to synchronisation tapping. Since the beta band is thought to be an internal representation of time (Fujioka et al., 2012) and reflects the degree of internal timing of motor movements (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2015), the current data suggest that syncopation requires a greater degree of internal timing than synchronisation. This finding is consistent with previous work showing that syncopation places more demand on the systems governing self-timed movements (Jantzen et al., 2004; Mayville et al., 2002). Such a difference in beta band oscillations may arise because synchronisation involves tapping in time with a beat where the accuracy is very clearly defined. In contrast, syncopation

requires the subjects to tap between the beats. Because the precise time at which to tap is not marked by an external stimulus, syncopation requires participants to have an internal estimation of the precise time at which they should tap. Accordingly, syncopation places greater demands on systems governing internal timing. This is manifested in a greater degree of beta band oscillation. The contention that AWDS recruit internal timing mechanisms during a task that involves some form of external stimuli may be somewhat puzzling at first glance. However, it is important to note that structures (such as the basal ganglia) involved in internal timing are also engaged during external timing tasks (see Chauvigné et al., 2014, for a meta analysis). In the left and right auditory cortex, AWDS showed significant differences between synchronise and syncopate.

9.4.5 AWS Within Group Differences

AWS showed some differences in the level of beta band activity in the left sensorimotor cortex for both the synchronisation and syncopation tasks. At first glance it seems that synchronisation rather than syncopation has larger peaks and troughs in beta band activity (see **??**). It should be acknowledged that this runs counter to our hypothesis. However, closer inspection reveals that the difference between beta oscillations in the synchronise and syncopate conditions is more likely to reflect a temporal difference in the beta envelope rather than an absolute difference in amplitude of beta band activity. Given the relative similarity in the amplitude of the response, this finding agrees with the idea that AWS found synchronisation and syncopation to be equally difficult (or perhaps it reflects a ceiling effect in AWS). In

the left but not right auditory cortex, AWS showed significant differences between synchronise and syncopate. The reasons why this occurred is not entirely clear. Interestingly, a reduction in the right auditory cortex is a marker of 'state' stuttering (Belyk et al., 2015). While the AWS were not stuttering (as the task did not involve vocalisation), the lack of beta modulation in the right auditory cortex perhaps indicates some relationship between timing and stuttering. This is something that could be explored in further research.

9.4.6 Between Group Differences

Synchronisation Tapping: During the synchronisation phase, it was found that AWS exhibited higher peaks and deeper troughs in the beta envelope than AWDS in the left sensorimotor cortex. In contrast, there were no differences in beta oscillations between AWS or AWDS in either the left or the right auditory cortex. This provides the first direct evidence that AWS and AWDS differ in neurological measures on a simple paced finger-tapping task even in the absence of behavioural differences.

Because this study did not find a difference in behavioural performance of AWS and AWDS our findings seem to be at odds with recent work showing CWS are poorer than CWDS at tapping to the beat (Falk et al. 2015; Olander et al. 2010 and see also Neef et al. 2011b) or discriminating between rhythms (Wieland et al., 2015). This discrepancy may partially be attributable to testing AWS rather than CWS. AWS may have compensated for deficits in timing by using regions such as the right inferior frontal gyrus (Preibisch et al., 2003). Although somewhat speculative at this point, differences in behavioural performance among CWS and CWDS on

finger tapping tasks may be arise because of differences in beta band oscillations.

If neural oscillations in the beta band index the difficulty of a movement (Andres et al., 1999; Müller et al., 2000) AWS may have found the synchronisation task harder to execute than AWDS. The current data suggest AWS found it more difficult to time movements to a metronome than AWDS: To achieve the same degree of behavioural performance as their fluent peers, AWS had to engage the sensorimotor cortex to a greater extent and this could reflect the fact that AWS have difficulty initiating simple movements. It is possible that the increased levels of beta band activity in AWS relative to AWDS reflects some form of compensatory activity rather than being causally related to stuttering.

The contention that AWS have difficulty in initiating movements is supported by transcranial magnetic stimulation studies. These studies indicate AWS have an elevated motor threshold relative to AWDS (Alm et al., 2013; Busan et al., 2013; Sommer et al., 2003, 2009) in the hand and mouth representation of the motor cortex. Generalising from manual movements to vocal movements (i.e. speech) should not be done without extreme caution. However, it is interesting that during speech, beta oscillations spread from the mouth representation of the motor cortex to the hand area of the motor cortex in AWS but not AWDS (Salmelin et al., 2000).

The fact that the differences in beta oscillations between AWS and AWDS are located in the left sensorimotor cortex is interesting in light of previous neuroimaging research on stuttering. A number of studies have identified structural and functional abnormalities in the left sensorimotor cortex of AWS. For example, Salmelin et al. (2000) used MEG to show that the sequence of activation of speech motor areas

(including the sensorimotor cortex) was normal in AWDS, but reversed in AWDS. Later work by Sommer et al. (2002) found that AWS had reduced white matter integrity in the left sensorimotor cortex. The level of neural activity in this region as measured by fMRI is also reduced in AWS during speech relative to AWDS (Watkins et al., 2008). That this study observed functional differences in neural oscillations in the beta band in the motor cortex is in keeping with finding cortical abnormalities in motor and sensorimotor regions of the brain in AWS relative to AWDS.

Syncopation Tapping: Interestingly, no significant differences were found in beta band activity between AWS and AWDS in any cortical regions during the syncopation task. This was somewhat unexpected because syncopation is generally thought to be more demanding than synchronisation (Jantzen et al., 2004) and should therefore be more likely to elicit differences between groups. The results perhaps suggest that syncopation was particularly demanding on both groups. Perhaps both AWS and AWDS were both pushed to their limit of their rhythmic performance. Accordingly, this is manifested in a particularly high level of beta band activity across both groups.

9.5 Limitations and Conclusion

One limitation of the present work is that only neural oscillations were examined in the beta band in a limited subset of brain regions. My investigation of neural oscillations was confined to these regions because they are frequently engaged in paced finger tapping (Chauvigné et al., 2014; Witt et al., 2008) and were therefore most likely to exhibit differences between AWS and AWDS. However, previous work

has identified a widespread network of other cortical and subcortical regions such as the cerebellum, basal ganglia and right inferior frontal gyrus that are often involved sensorimotor synchronisation (e.g. Jantzen et al., 2004; Mayville et al., 2002; Pollok et al., 2009). MEG has considerable difficulty in detecting activity of subcortical regions like the basal ganglia (Krause et al., 2010). While several authors have demonstrated detecting activity from this source is possible (David et al., 2011; Fujioka et al., 2010; Krause et al., 2010; Ng et al., 2013) I wanted to record signals that would be easy to detect. Given the involvement of the basal ganglia in stuttering (Alm, 2004; Civier et al., 2013; Chang and Zhu, 2013), rhythm (Grahn et al., 2007; Grahn and Rowe, 2009) and the origins of the beta band (Bartolo et al., 2014; Bartolo and Merchant, 2015; Sen et al., 2010; te Woerd et al., 2014), it would be interesting to examine whether there are differences between AWS and AWDS in the neural oscillations of the beta band in the basal ganglia during synchronisation and syncopation tapping.

A second limitation of this study is the heterogeneity in the measured severity of stuttering amongst the AWS that were tested. Since stuttering severity was measured by means of a ten minute speech sample rather than by using the stuttering severity index. No attempt was made to measure correlations between the percentage of stuttered syllables and either MAD's/tap to tone asynchronies or neural oscillations in the beta band. It should be noted that stuttering severity can vary considerably over the course of a single day between and within individuals (Karimi et al., 2014). Thus the heterogeneity of our sample is perhaps reflective of the variability in severity in AWS. It may be concerning that some participants exhibited a very small percentage of stuttered syllables. One possible reason for this is because

AWS may have been employing techniques to minimise their stuttering. Indeed, this study made no attempt to prevent the use of fluency inducing techniques during collection of the speech sample. Additionally, while all participants were observed to stutter during their time in the lab, the true extent of this stuttering was not always evident on the voice recording. Interestingly, recent work has shown that estimating the percentage of stuttered syllables is up to 18% higher when using audiovisual recordings as opposed to audio recordings alone (O'Brian et al., 2015).

Although I do not consider it a limitation, I also wish to address concerns about the lack of behavioural differences between groups. As described in the introduction, a simple task was deliberately used so that there would be no behavioural differences. This would mean that any differences in neural activity was not confounded by differences in behavioural performance. The fact that atypical beta band oscillations were found in AWS compared to AWDS in the absence of behavioural performance, suggests that the neural processes underlying the timing of movement is abnormal in AWS. I believe that the lack of behavioural difference is therefore a strength of my study. Nevertheless, employing a more difficult task such as tapping with the non dominant left hand will create more extensive differences in neural activity (François-Brosseau et al., 2009) between AWS and AWDS that may or may not be accompanied by differences in behavioural performance. Further, the effect of synchronising or syncopating more difficult vocal or manual movements on the neural activity of AWS and AWDS remains to be investigated by future research.

The present study showed that AWS and AWDS exhibit marked differences in the modulation of the beta band envelope in the left motor cortex. This occurs

in the absence of differences in overt behavioural performance between AWS and AWDS. Future research may wish to examine differences in other frequency bands associated with timing or movement in a wider network of regions or in other tasks involving timing and rhythm in AWS. It would also be interesting to examine beta band activity during the production of rhythmic movements or the perception of rhythmic tones in CWS.

Chapter 10

Neuromagnetic Beta Band Responses of Typically Developing Children to Isochronous Intervals

10.1 Introduction

Fluent speech is a central component of our everyday communicative interactions. This communication is governed by a hierarchical neural system that enables the sequential and contiguous production of segments of speech. A requisite function of this system therefore, is to facilitate the intricate and accurate production of temporal intervals. There is increasing interest in the putative link between rhythmic ability and language. A growing body of evidence suggests that the ability of the brain to inherently track rhythm is an important determinant of the perception and production of fluent speech (Peelle and Davis, 2012). For example, it has been shown that in young children, rhythmic aptitude is an important predictor of language fluency (Strait et al., 2011) and similarly that training in rhythmic abilities increases language fluency over and above traditional classroom activities (Taub and Lazarus, 2013). In much the same way, the ability to track rhythmic sounds appears to be associated with the production of fluent speech, it also appears to be the case that difficulties in tracking rhythmic sounds is associated with difficulties in producing and perceiving fluent speech. This is highlighted by the fact that regular external stimuli aid language fluency in a variety of developmental language disorders such as stuttering (Toyomura et al., 2011), dyslexia (Thomson et al., 2013) and specific language impairment (Przybylski et al., 2013)) in both adults and children. Thus, there appears to be a relationship between rhythmic ability and language fluency, although the neural mechanisms underlying such phenomena in young children are poorly understood. Before investigating any relationship between rhythmic tracking abilities and the onset of developmental disorders, it is first necessary to establish

whether typically developing young children exhibit neural activity that entrains in a rhythmic fashion.

Studies investigating the rhythm tracking abilities of children have tended to focus on either one of two areas: the production of rhythm and the perception of rhythm. Behavioural studies show that older children (10 years, 8 months) are able to tap in time (Thomson and Goswami, 2008) or make oral motor movements (LaGasse, 2013) in time with regularly occurring sounds. This ability appears to improve as children mature (Drake et al., 2000; Malbrán, 2002).

Children are readily able to detect auditory regularities. For example, as early as 7 months of age, behavioural studies show that children are readily able to discriminate between different rhythms (Phillips-Silver and Trainor, 2005). Children are able to recognise and detect rhythm changes in tempo and can identify omissions in a regular train of sounds (Honing et al., 2009; Winkler et al., 2009). However, while there is a relative abundance of behavioural studies documenting rhythm perception behaviourally in children and infants, there is far less information regarding the neural processes underpinning rhythm perception.

Dynamic Attending Theory (DAT) is a framework for understanding how the brain processes rhythm. According to this theory, the brain focuses attention on important points in time by aligning internal (neural) oscillations with external stimuli (Large and Jones, 1999). A wide variety of neural oscillations in distinct frequency bands have been implicated in the processing of rhythm (see for review (Arnal and Giraud, 2012)). For instance, the gamma band has been related to the anticipation and perception of rhythmic meter (Zanto et al., 2006). The alpha band

(8-12Hz Rohenkohl and Nobre, 2011; 8-14Hz Thut et al., 2006) is desynchronised when a predictable stimulus is expected. Oscillations in the delta range align with predictable rhythmic stimuli such as isochronously presented tones (Nozaradan et al., 2011) and speech (Giraud et al., 2007). A growing body of literature has associated the beta band (12-30Hz) with the internal representation of isochronous intervals (e.g. Fujioka et al., 2012). The authors of that study presented adults with trains of sounds occurring at isochronous intervals of 390, 585 or 790ms, or a random condition in which the inter-stimulus interval varied randomly between 390 and 790ms. Fujioka et al. (2012) compared the timing of the descending slope of the beta band and the rising slope of the beta band across conditions. Whereas the descending slope of the beta band was the same across conditions, the rising slope of the beta band peaked close to, or before stimulus onset in the rhythmic condition. In contrast, the effect was much less prominent in the random condition. This led the authors to conclude that the rhythmic modulation of the beta band envelope was a reflection of the internal representation of temporal intervals. Since that time, this finding has been backed up by a other studies which have found the beta envelope to be associated with the accuracy of predicting deviations in temporal (Arnal et al., 2014) intervals and focusing attention on upcoming beats (Todorovic et al., 2015). The fact that neural oscillations in the beta band are associated with the internal representation of auditory intervals is particularly interesting because it is traditionally associated with movement. Indeed beta band power is known to decrease when executing, imagining or observing a movement before increasing (rebounding) to normal levels once the movement becomes stable (Burianová et al., 2013, 2014; Kilavik et al., 2013). Thus neural oscillations in the beta band may be particularly important for the ability to

perform rhythmic or quasi-rhythmic movements such as speech.

Recent work using electroenephalography (EEG) has demonstrated that it is possible to record induced beta band oscillations from children around the age of 7 years old (Cirelli et al., 2014). This study found that while children's beta band activity peaked at around the onset of the sound for slow paced tempi (585ms and 780ms SOA), the entrainment response was not evident at a faster tempo (390ms SOA). The choice to use EEG over MEG in the Cirelli study (cf. Fujioka et al., 2012) was driven by methodological considerations, as it can be particularly difficult for children to remain still for an extended period of time required for such an experiment. Head movement within the MEG environment can be problematic because MEG relies on measuring brain activity from fixed sensor positions relative to the position of the head. In contrast to this, EEG relies on measuring signals from electrodes that are fixed to the scalp and is thus more tolerant of movement. The overriding factor in using EEG over MEG for experiments on young children however is that many institutions do not have an MEG specifically designed for children (e.g. Sowman et al., 2014). Another important difference between MEG and EEG is that they are sensitive to different sources. MEG is able to detect activity in tangentially oriented neurons, but not radially oriented neurons. EEG in contrast is sensitive to both. The difference in this sensitivity may contribute to differences in the measured neural oscillations in the beta band. Further, MEG has a better spatial resolution than EEG and source localisation is likely to be more accurate.

There are a number of outstanding questions regarding the characteristics of beta entrainment to rhythmic sounds in children. First, it is unknown whether it

is possible to record neuromagnetic beta band responses from typically developing children in response to isochronous intervals. Thus, one aim of the current study was to determine the feasibility of recording beta band responses to isochronous rhythms in children between the ages of 4 and 13. Since there is already some evidence that adults (Fujioka et al., 2012) and children (Cirelli et al., 2014) exhibit a predictive peak in the beta envelope before the onset of isochronously presented sounds, it was expected to be able to replicate this finding with MEG in typically developing children. Secondly, while the beta band peaks at the onset of isochronous sounds, it does not definitively prove the existence of an internal representation of tempo. If a child has internalised the temporal interval, then they should also exhibit a response when the expected stimulus occurs earlier or later than expected. Specifically, I expected that this would be manifested through an increase in evoked activity after an unexpected change in tempo.

10.2 Method

10.2.1 Participants

17 typically developing children (14m 3f) aged 3 to 11 years (M = 8.4 ± 2.68 years) participated in this study. Parents reported that none of their children had any history of speech, language or hearing difficulties. Normal hearing thresholds were confirmed between 500Hz and 2000Hz and normal language skills as measured by criterion score on one of two standardized tests: the Preschool Language Screener (PLS-4, I. L. Zimmerman et al., 2002) or the Clinical Evaluation of Language Fun-

damentals (CELF-P2; Semel et al., 2006). A parent or guardian provided written informed consent for their child's participation before the experiment began and the participant received cash payment and a toy for their involvement. This study was approved by the Macquarie University Human Research Ethics Committee (see Appendix E for final approval).

10.2.2 Stimuli

Participants were presented trains of isochronous auditory tones (60ms (5ms rise and fall times) 262Hz sinusoidal tones created in Audacity 2.00 ($http://audacity.sourceforge.net$ The stimulus onset asynchronies (SOA) used were 390ms, 585ms and 780ms (equivalent to stimulus rates of 2.5, 1.7 and 1.3 respectively). These tempi were selected for two reasons: First because detecting differences in tempo is optimal in the range of 1-3Hz (Drake et al., 2000) and second because these are the same stimuli and intervals used in previous research by Fujioka et al. (2012) and Cirelli et al. (2014). There was however one important difference between the current study and the aforementioned studies: In the rhythmic condition in the current study, participants were presented with a continuous train of sounds in which the SOA would stay constant for 5-10 tones before changing to a different SOA. The tones were pseudo randomised in such a way that each stimulus sequence contained the same number of tones and changes to a new tempo. The reason for this difference in experimental design is because I wanted to compare the evoked response to changes in tempo as well as the induced response to isochrony. The random condition was identical to the rhythmic condition except for the fact that the SOA changed randomly after each tone (rather than

after every 5-10 tones). To ensure comparability between conditions, the number of transitions between each SOA (e.g. 585ms to 780ms and vice versa) was maintained the same. For each tempo there was a total of 575 sounds (excluding the first tone in each sequence). Sounds were presented through a speaker (Panphonics) placed at the foot of the MEG plinth. Stimulus intensity was set to 75 dB SPL as measured from the MEG dewar. All stimulus sequences were presented via a Dell Pentium 4 computer running Windows 7 using Presentation 16.3 (Presentation Neurobehavioral Systems, Albany, USA).

10.2.3 MEG recording

Neuromagnetic responses were recorded using either a custom built paediatric MEG (Model PQ125R-N2, KIT, Kanazawa, Japan) consisting of 125 coaxial first order gradiometers with a 50mm baseline or a system built for adults (and older children) consisting of 160 coaxial first order gradiometers (Model PQ160R-N2, KIT, Kanazawa, Japan). Notably the two systems had the same gradiometer specification and were in the same magnetically shielded room: thus the amount of noise affecting the two systems was comparable. Prior to MEG measurements, five marker coils were placed on an elasticized cap on the participant's head and their positions and the participant's head shape were measured with a pen digitizer (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing marker coils in the MEG dewar both before, and after the recording session. Participants whose head movement exceeded an average threshold of 7 mm were excluded from further analysis. During recording, the children lay supine with their arms by their sides

whilst watching a silent movie of their choice. Additionally, to ensure the younger participants were comfortable and did not move excessively, a researcher sat with them at all times throughout the experiment. Children were monitored from outside the magnetically shielded room by simultaneous video and audio to ensure they did not synchronise movements with the auditory tones. The total duration of the recording session was 33 minutes.

10.2.4 Data Analysis

Data were analysed using SPM12 (Wellcome Institute, London, UK) running on Matlab R2014a (The MathsWorks, Natrick, USA). The raw data was sampled at a continuous rate of 1000Hz. Once it had been collected, the data was down-sampled to 250 Hz, resulting a temporal resolution of 4ms. This signal was then band-pass filtered from 1 to 40 Hz. The MEG epoch extracted for analysis was -800 ms to 1100 ms after the tone onset, identical to the intervals used by Fujioka et al. (2012). SPM12's fieldtrip visual artefact rejection function was then used to remove all trials containing amplitudes that had Z values of greater than 2. Using this method, less than 5% of trials for any condition were excluded. There were a total of 585 tones in each isochronous condition and 45 changes for every tempo in each direction (e.g. 45 changes from 585 to 390 and 45 changes from 585 to 780).

10.2.5 Auditory Dipoles

Virtual sensors were constructed using the following procedure. The trials in the random condition were used solely for the purpose of localising dipoles as this condition

was independent of the rest of the data (i.e. the rhythmic conditions). First the trials in the random conditions were averaged and then the global field power calculated. Next the grand mean of the evoked response across all subjects was calculated and found the time of the peak of the M100, the MEG equivalent of the N100. A 20ms window centred on this time point (i.e. 90-110ms) was then used to define the time of maximum amplitude of the evoked response for each individual participant. This time was then used to localise the equivalent current dipoles (ECD). These dipoles were fitted within a 40ms time window (± 20ms either side of the peak amplitude time) and allowed to freely orient within a 100mm sphere. There were a total of 10 iterations to determine the optimal position of the ECD. The seed coordinates of the left and right auditory dipoles were located in Heschl's gyrus (MNI -40,-21,9) and (40,-21,9). The average MNI coordinates of the left and right auditory dipoles for all participants was (-37,-21,8) and (36,-23,9) respectively and can be seen in Figure 10.1.

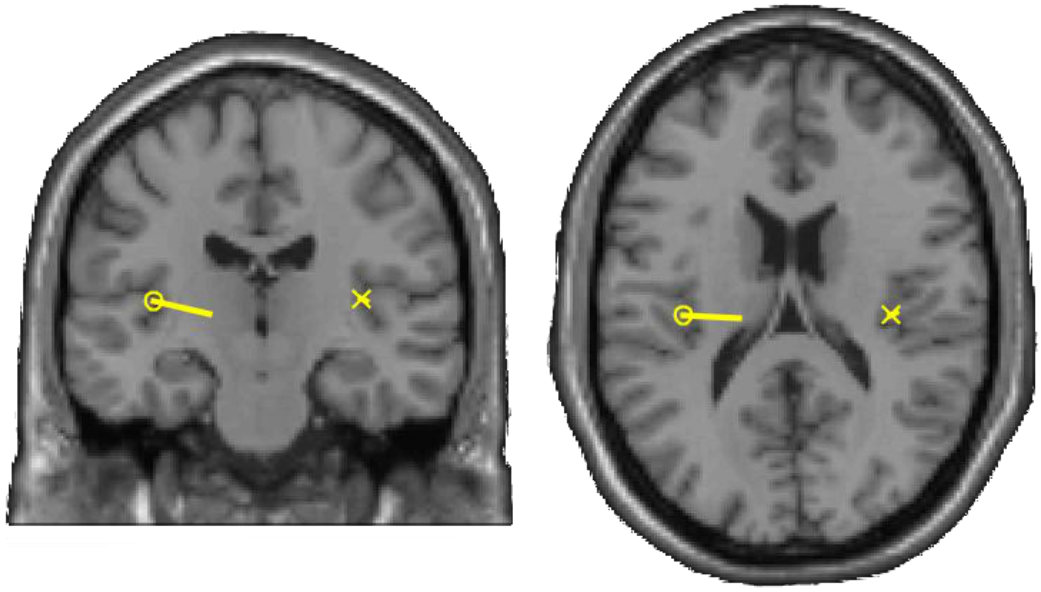

Figure 10.1: Average location and orientation of the equivalent current dipoles in the left and right auditory cortex.

10.2.6 Evoked Responses

Zero-phase root mean square (RMS) smoothing was applied (moving window of 5 samples with a consecutive overlap of 4 samples) to mean virtual sensor data for the left and right auditory cortex for each participant in order to remove the polarity of the response which could vary between participants depending on the optimal orientation of the dipole. The smoothed data was then cropped in the time domain to 0 to 400ms (as this was close to the minimum isochronous interval of 390ms). The reason the activity before the onset of the change was not examined was because the preceding tones occurred at different stimulus onsets. The effect of the differences in the preceding interstimulus interval in the prestimulus epoch would therefore create spurious differences in the prestimulus time. For this reason activity is only examined after the onset of the tone, then the difference between the response for each tempo

change (i.e. 390ms to 585ms, 390ms to 780ms, 585ms to 790ms and vice versa) and the 4th tone after the establishment of the new tempo (e.g. the difference between the change from 585ms to 390ms and the 4th tone in the 390ms tempo) were calculated. For ease of reference, I refer to this as the tempo mismatch response. Notably, this analysis approach is similar to Háden et al. (2015) who compared how changes in tempo affected the evoked response in infants. It was expected that there might be differences in how the brain responds to changes from a faster tempo to a slower tempo and vice versa.

All statistical testing was implemented using non-parametric point-by-point comparisons using the non-parametric permutation statistics implemented in the std$_s$tat function of EEGLAB (Delorme et al., 2006). All tests are corrected using the false discovery rate (FDR; Benjamini and Yekutieli 2001) approach unless otherwise specified. I first used paired t-tests to compare the amplitude of the tempo mismatch response between the left and right hemispheres. The same statistical tests were applied to the analysis of each tempo mismatch responses in the lengthening conditions (390ms to 780ms vs. 585ms to 780ms vs. 390ms to 585ms). There were no significant differences between mismatch responses across tempi in the shortening condition or the lengthening condition (corrected for false discoveries at $p>0.05$). Consequently, I collapsed across the mismatch responses within condition (shortening or lengthening) for each tempo. The resulting data thus contained average of the mismatch responses for each tempo in the both the left and right hemisphere. These were then submitted to one sample t-tests comparing the amplitude of the tempo

mismatch response to zero across the epoch of 0 to 400ms (i.e. 10ms longer than the shortest tempo).

10.2.7 Correlation of evoked responses and age

I was interested in examining possible relationships between age and mismatch response. To examine this, non-parametric (Spearman) correlations were conducted between measures of age and the maximum amplitude of the tempo mismatch response in the left and right hemispheres.

10.2.8 Induced Responses

Time-frequency decompositions on virtual sensor time series were calculated separately for each individual, hemisphere and stimulus condition from 1-40Hz using a Morlet wavelet transform (Bertrand et al., 1994) and averaged across trials. The averaged plots were then cropped in the time domain from -500 to 800 ms so as to reduce artefacts occurring at the edge of the spectrogram. The data was rescaled to the mean frequency across the entire epoch. For statistical analysis, and to illustrate the change in beta power across conditions, I collapsed the full frequency spectra across three different frequency ranges. In order to be able to compare our results to previous work (Cirelli et al., 2014), it was averaged across 15-20Hz (the optimal range they found for children) and across 20-25Hz (the optimal range they found for adults). Furthermore, visual inspection of the time frequency spectograms in their publication revealed that there appeared to be beta modulation in a lower frequency range: 12-15Hz (see Figure 10.2). Therefore I also collapsed across 12-15Hz. Be-

fore proceeding with further statistical analysis, paired t-tests were used to examine whether there were any differences in beta modulation between the left and right hemispheres. Since there was no significant difference (using a false discovery rate (FDR) rate of $p<0.05$), beta modulation was averaged across the left and the right hemispheres. One sample t-tests were used to compare whether beta modulation in the 390, 585 and 790ms condition was different from zero. The epochs used for each comparison differed depending on the condition. The beta modulation in the 390, 585 and 780ms conditions were compared to zero between timepoints of 0-400ms, 0-600ms and 0-800ms respectively. Notably, this the same approach adopted by Cirelli et al. (2014). During analysis, 10,000 permutations were run comparing the time point of each isochronous condition to zero at a lenient threshold of $p=0.05$ uncorrected (as per Cirelli et al. 2014) and a more stringent threshold using a FDR corrected threshold of $p<0.05$. These tests were run separately for each frequency range (20-25Hz, 15-20Hz and 12-15Hz).

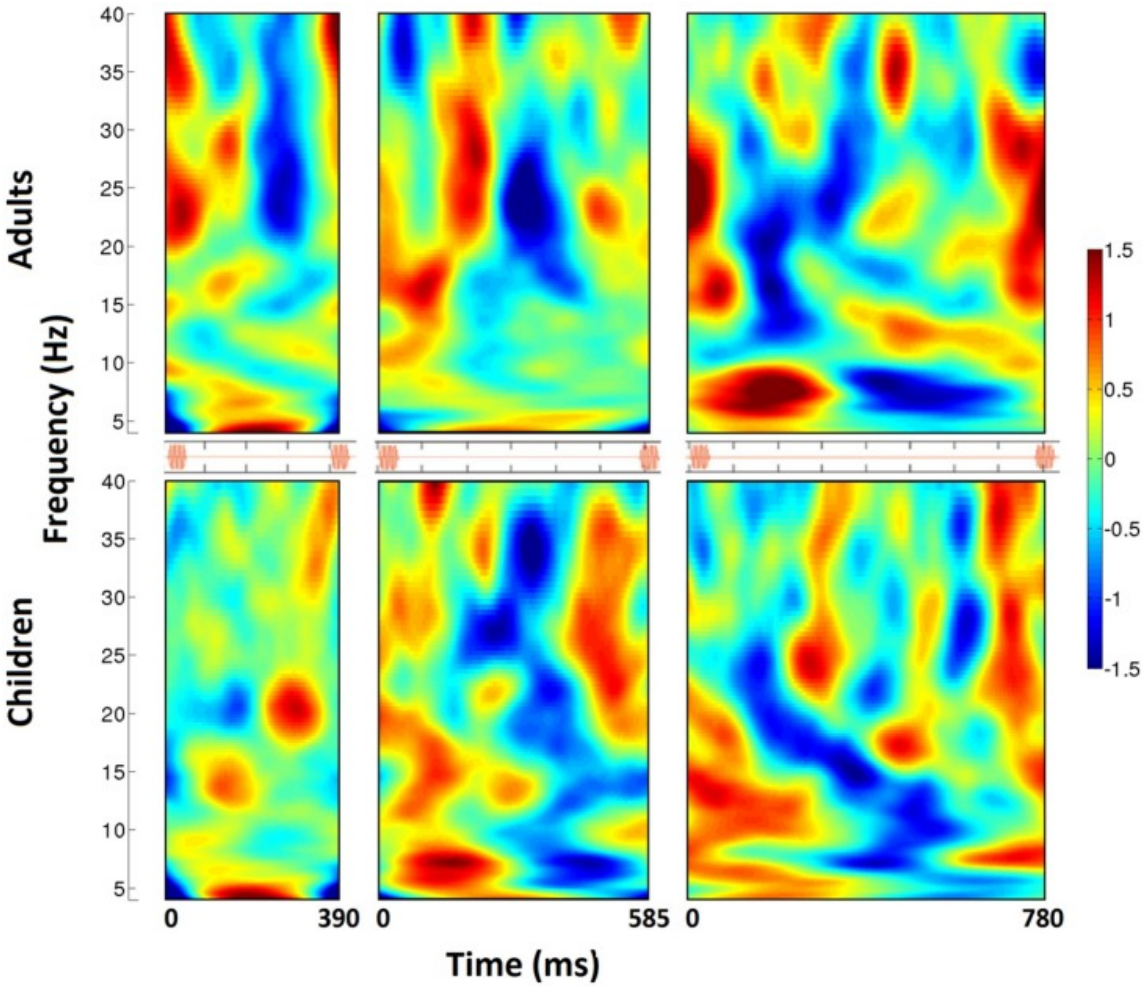

Figure 10.2: Time Frequency Spectograms from Cirelli et al. 2014. The time-frequency spectrogram of percent power changes from right auditory cortex spatial filter for three tempo conditions (390, 585, 780 ms from left to right). Adults are shown on the top, and children on the bottom. Analyses span from tone onset to subsequent tone onset, as visualized in the orange stimulus onset indicators for each tempo condition. From the spectrograms, a pattern of induced beta-band desychronization (negative percent change values) following each tone and a rebound (positive percent change values) before the onset of the next beat can be visualized. The timing of this pattern varies across tempo, and is stronger and more consistent in children compared to adults (Figure reproduced with permission from Cirelli et al. 2014 under open access agreement).

10.2.9 Correlation of induced responses and age

To examine whether the peaks in beta band activity were related to the age of our participants, Spearman correlations were performed between the point of maximum beta amplitude for each isochronous condition in the first 400ms and age. Since

the lower frequency band (12-15Hz) revealed the most extensive differences in the time frequency data (i.e. the greatest number of contiguous time points where beta power was significantly different from zero across most isochronous tempi), I only conducted the correlation between beta amplitude in the 12-15Hz range.

10.3 Results

10.3.1 Evoked Data

This analysis was undertaken using a statistical threshold of $p<0.05$ corrected for false discoveries (FDR corrected) to determine if the mismatch response was different from zero.The one sample t-test revealed the tempo mismatch response was significantly different from zero in the right hemisphere across multiple contiguous time points between 136ms and 152ms and also between 220ms and 320ms. Similarly, there were also marked differences between the mismatch response in the left hemisphere and zero between 292ms and 344ms (see Figure 10.4). Notably, there were no significant differences between the lengthening conditions and zero (not shown).

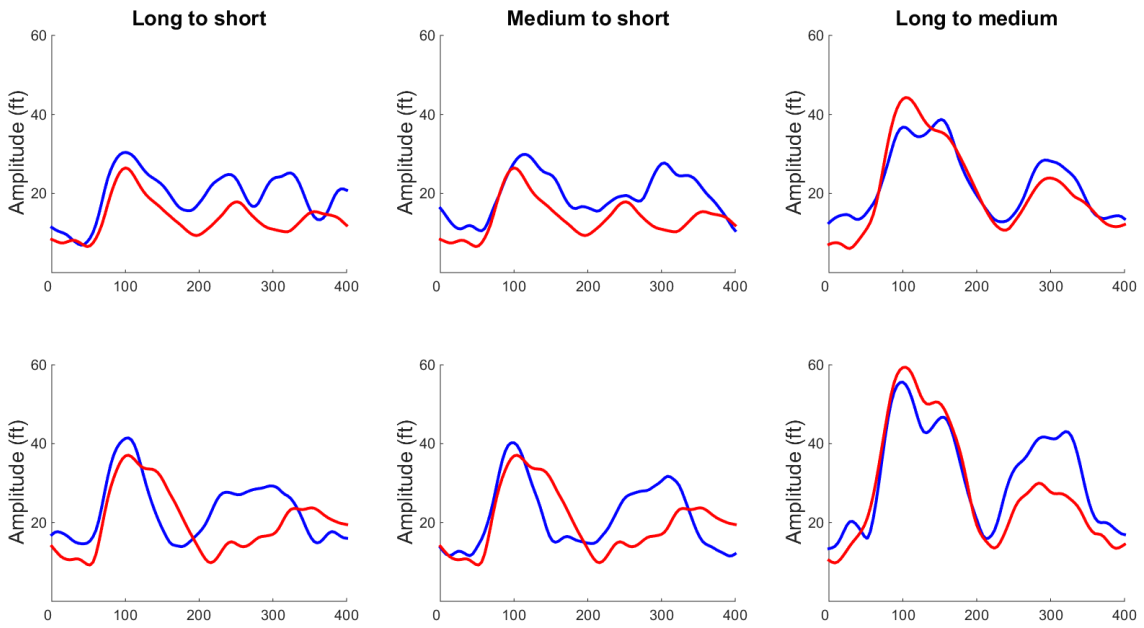

Figure 10.3: RMS evoked responses for the change and the 4th tone after the new tempo for the left and right hemisphere. The top row depicts the left hemisphere and the bottom row depicts the right hemisphere. The first second and third columns represent the different change types. In each graph, the blue line represents the change and the red line represents the 4th tone after the change.

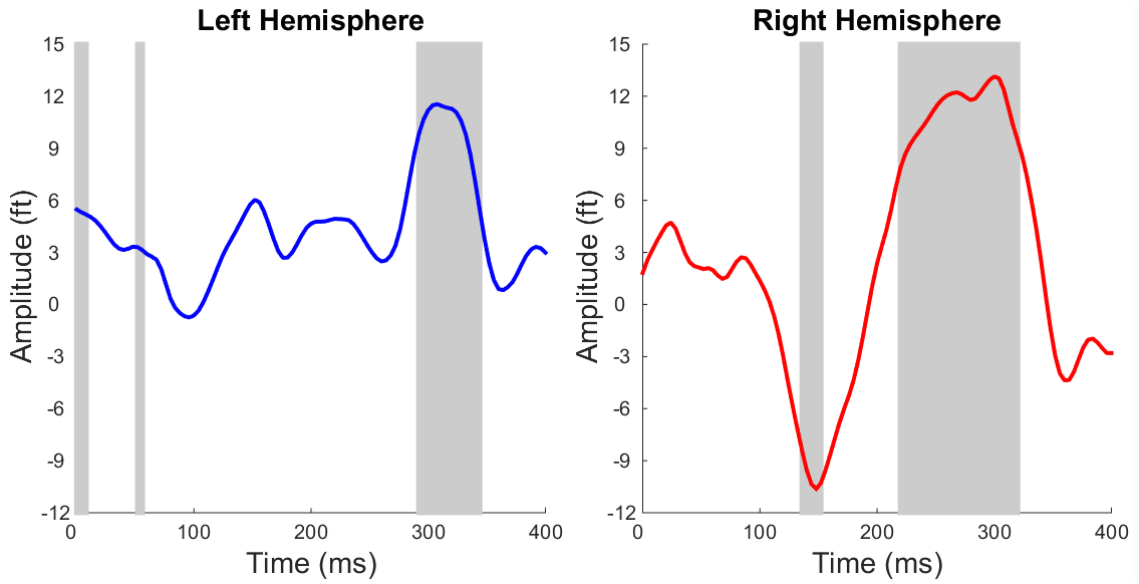

Figure 10.4: One sample t-test of the RMS evoked shortening contrast (i.e. the difference between the first stimulus in a new tempo and the tempo being changed to) for the left and right hemispheres respectively. The plots depict the comparison between 0 and 400ms. The dark grey represents significant differences at a strict threshold of $p<0.05$ FDR corrected.

10.3.2 Correlation of mismatch response with age

There was no significant relationship between the amplitude of the mismatch response in the left hemisphere and age $r=-0.245$ $p<0.343$, $n=17$ or between the right hemisphere and age $r=0.069$, $p<0.794$, $n=17$.

10.3.3 Time Frequency Data

The time frequency decompositions between 1-40Hz and -600 ms to 800ms peristimulus time can be seen in Figure 10.4.

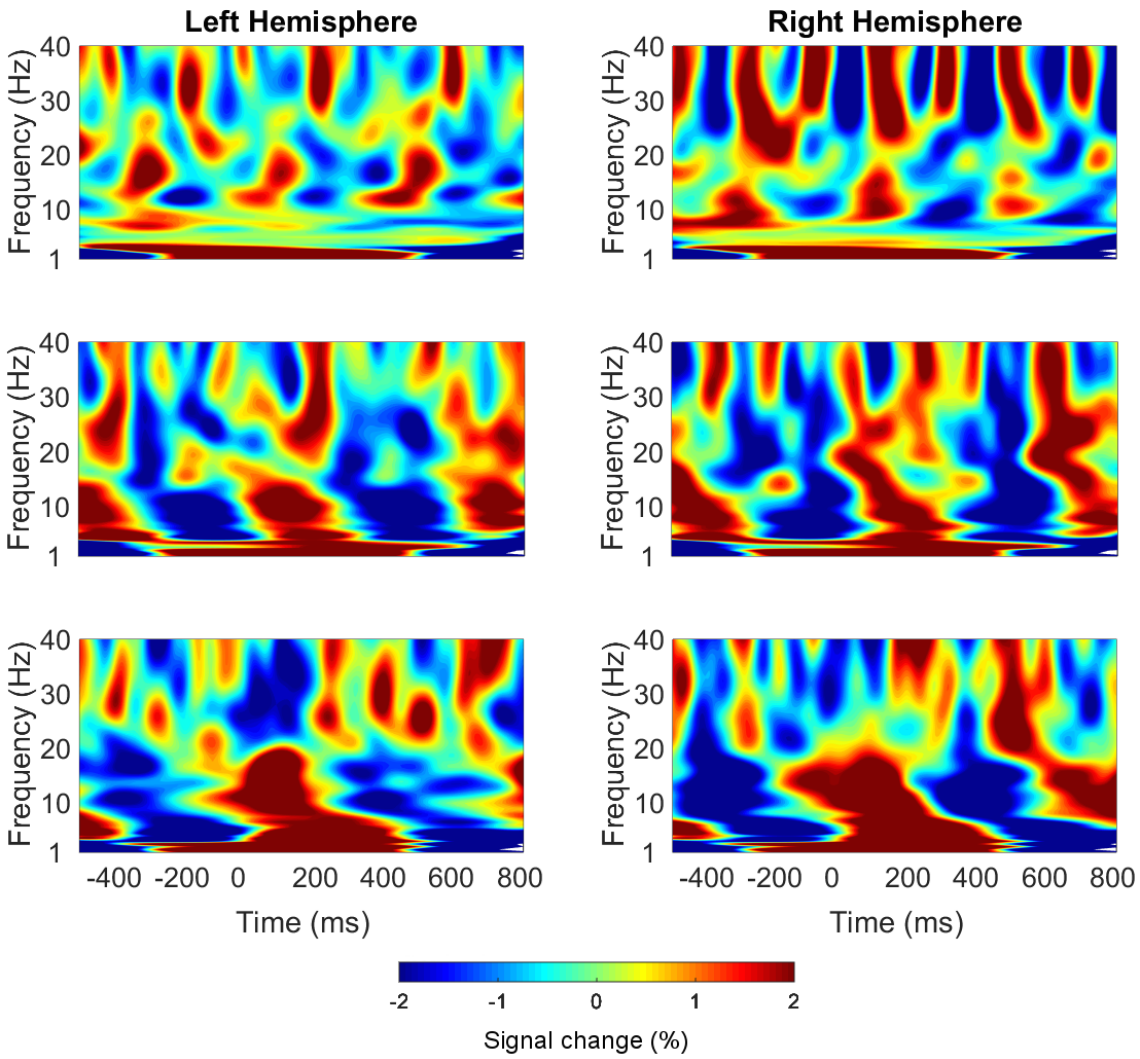

Figure 10.5: Time frequency spectograms and beta envelope for each rhythmic condition. The left and right columns depict the time frequency spectograms for the left and right hemispheres respectively. The first second and third rows depict the different tempos (390ms, 585ms and 78ms respectively).

The averaged beta modulation across different frequencies can be seen in Figure 10.6. The top, middle and bottom rows depict time frequency plots collapsed across 20-25Hz, 15-20Hz and 12-15Hz respectively (see Figure 10.6). In each panel, the blue line corresponds to the average signal percentage change from the mean of the entire epoch. The light grey corresponds to significant differences at uncorrected threshold of $p<0.05$ and the dark grey corresponds to significant difference at an FDR corrected threshold of $p<0.05$. There appeared to be the most extensive difference

in the lower beta band (12-15Hz). Specifically, the 780ms condition exhibited a significant peak in beta band envelope between 100-200ms. There was also a trough between 352ms and 516ms and finally another peak between 788ms and 800ms at an FDR corrected threshold of $p<0.05$. As would be expected, there was a slight increase in the range of significant time points when reducing the statistical threshold to an uncorrected value of $p<0.05$. For the 585ms condition, there was a significant peak between 68s and 152ms. And a significant trough between 436ms and 556ms also at a corrected threshold of $p<0.05$ FDR. The 390ms condition was not significantly different from zero for ant time point at the FDR corrected threshold level. There was however a significant peak between 68ms and 88ms when reducing the threshold to $p<0.05$ uncorrected (see Figure 10.6).

For a visual comparison of the beta band oscillations in the current study and previous work see Figures 10.6-10.7 from Cirelli et al. (2014) which depict the beta band activity in the 20-25Hz range and the 15-20Hz range for both adults and children. Note that the light and dark grey in our study represent significant at $p<0.05$ uncorrected and $p<0.05$ FDR corrected whereas the same colours represent $p<0.05$ uncorrected and $p<0.01$ uncorrected in the Cirelli et al. (2014) paper.

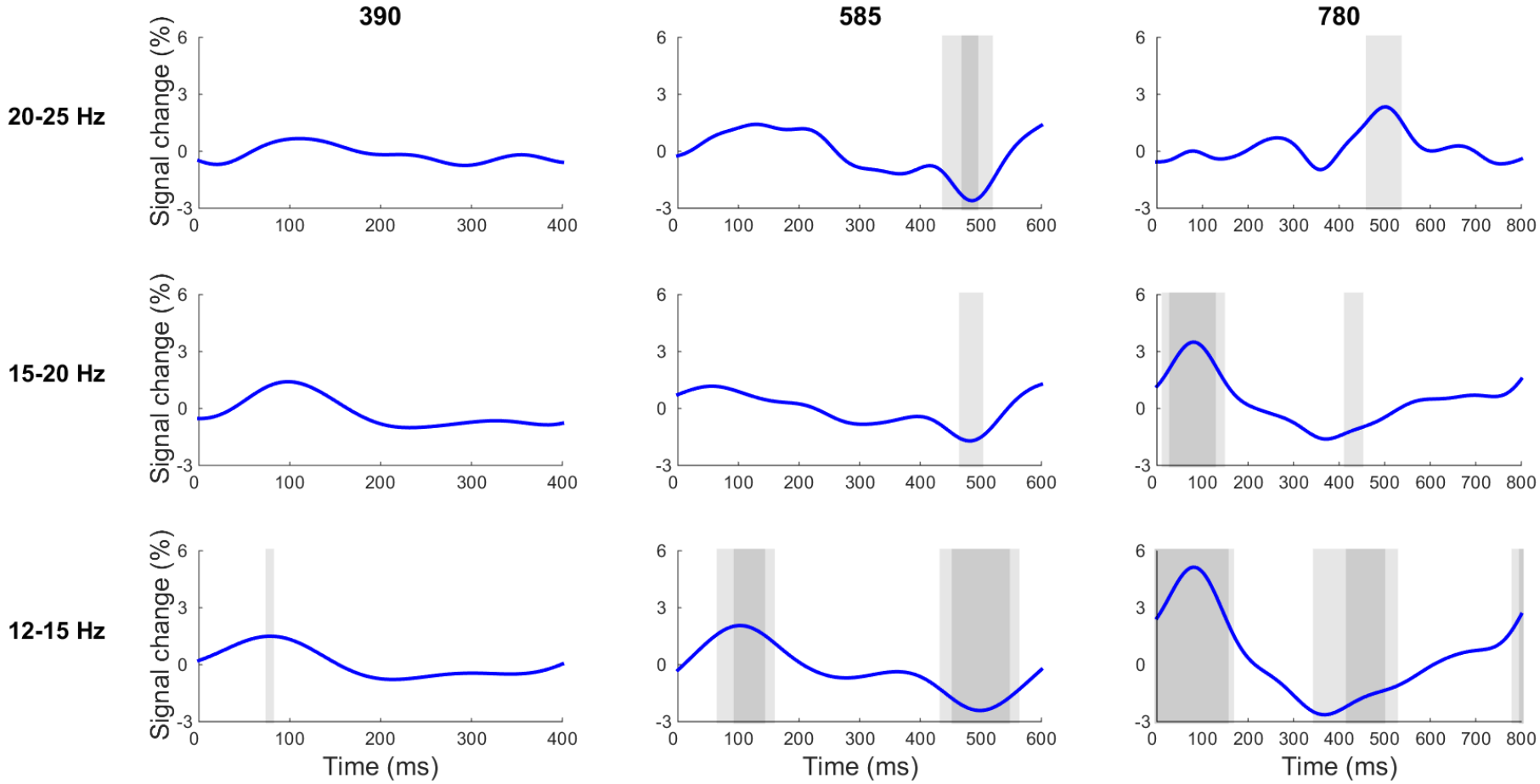

Figure 10.6: Averaged beta band envelope. The first second and third columns depict the average of the beta band envelope in the left and right hemisphere for the 390ms, 585ms and 780ms condition respectively. The top, middle and bottom rows depict the beta band activity collapsed across high beta band (20-25Hz), middle beta band (15-20Hs) and low beta band (12-15Hz). Note that each tempo is depicted on a different x-axis scale dependent on the tempo. The 390ms condition is shown between 0 and 400ms, the 585 condition is shown between 0 and 600ms and the 780ms condition is shown between 0 and 800ms. The light grey depicts significant differences from 0 at a relaxed statistical threshold of $p<0.05$ uncorrected and the dark grey depicts significant differences at a more stringent threshold of $p<0.05$ FDR corrected.

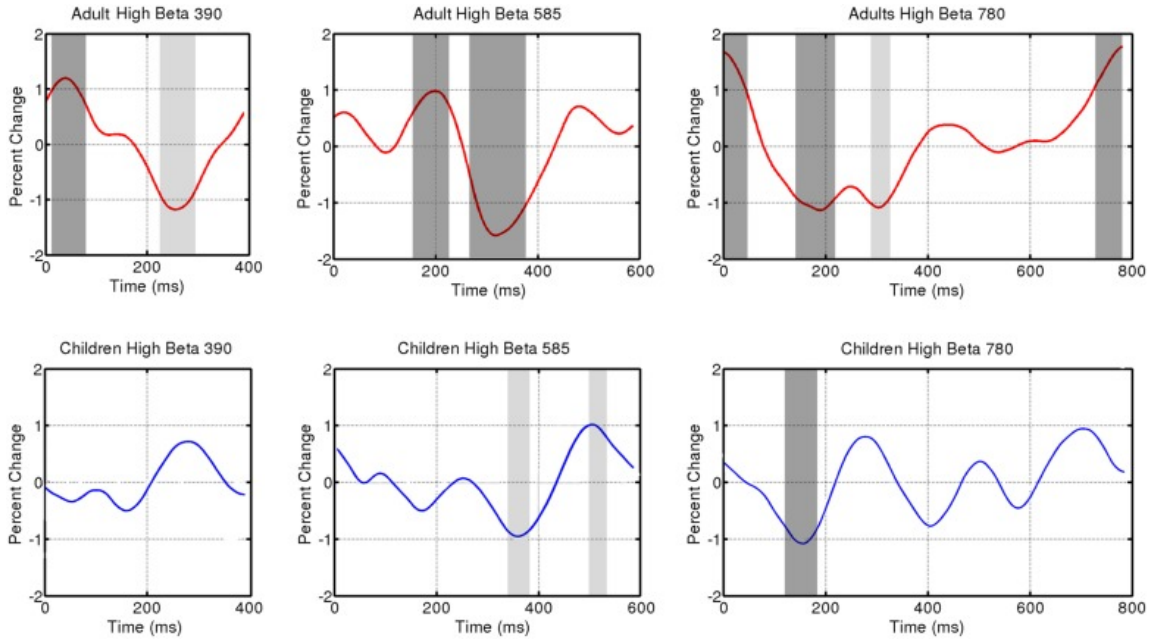

Figure 10.7: Induced power fluctuation in high beta (20-25 Hz) activity for the three tempo conditions (390, 585, 780 ms) and two groups (adults and children). Running one-sample t-tests were used to determine when group fluctuations differed from zero. Light grey represents $p < 0.05$. Dark grey represents $p < 0.01$. Figure reproduced with permission from Cirelli et al. (2014) under open access agreement

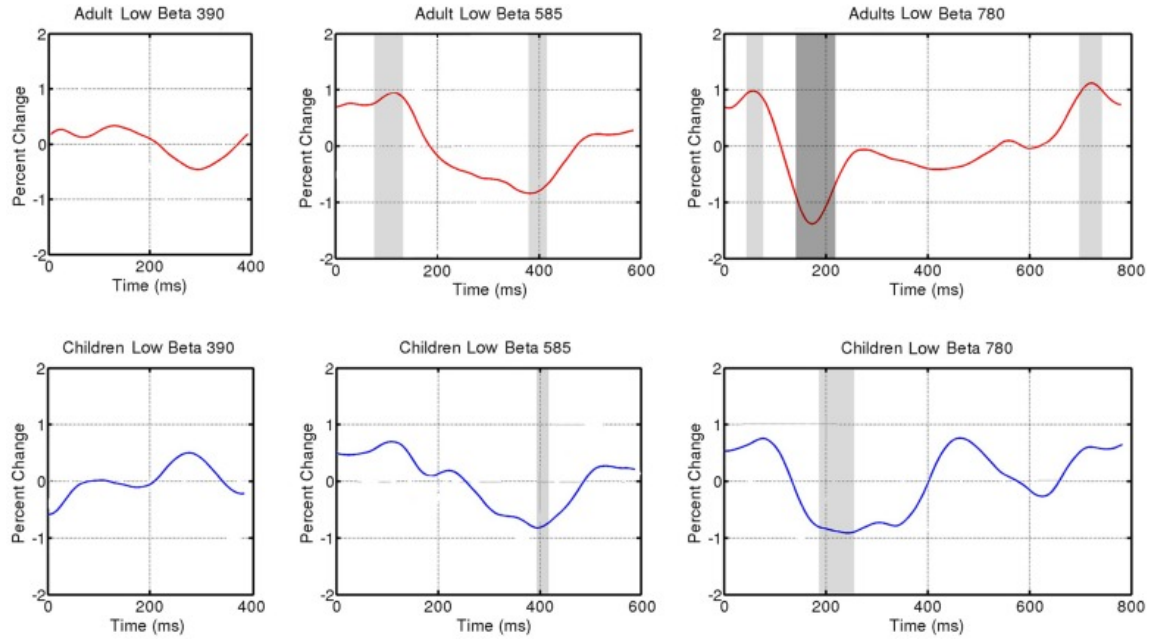

Figure 10.8: Induced power fluctuation in low beta (15-20 Hz) activity for the three tempo conditions (390, 585, 780 ms) and two groups (adults and children). Running one-sample t-tests were used to determine when group fluctuations differed from zero. Light grey represents $p<0.05$. Dark grey represents $p<0.01$. Figure reproduced with permission from Cirelli et al. (2014) under open access agreement.

10.3.4 Correlation of Age and Induced Responses

The greatest number of contiguous time points where beta band envelope was significantly different from zero was apparent in the 12-15Hz range. Therefore only correlations on beta envelope modulation in this frequency range were performed. Spearman correlations revealed that there were no significant correlations between age and beta band activity at the slowest or fastest tempo. Specifically, the correlation between age and the beta band activity for the 390ms condition was r=0.049, p=0.852, n=17. The correlation between age and the beta band modulation for the 780ms condition was r=0.277; p<0.282, n=17. There was however a significant correlation between the 585ms tempo and age (r=0.581, p<0.014, n=17).

10.3.5 Correlation of Induced and Evoked Responses

In order to explore the relationship between the evoked responses to the change and the induced beta band oscillations, Spearman correlations between the two measures were also conducted. There was no significant correlation between the tempo mismatch response in the left hemisphere and the 390ms condition (r=-0.56, p<0.830, n=17) the 585ms condition (r=-0.096, p<0.715, n=17) or the 780ms condition (r=-0.270, p<0.295,n=17). Likewise, there was no significant correlation between the tempo mismatch response in the right hemisphere and the 390ms condition (r=0.417, p<0.096, n=17) the 585ms condition (r=0.186, p<0.474, n=17) or the 780ms condition (r=0.022, p<0.933, n=17).

10.4 Discussion

The present experiment aimed to test the feasibility of recording neuromagnetic beta band oscillations from young children in an MEG setting and to determine whether or not children exhibited adult-like responses to isochronous stimuli. In line with my hypothesis, there were peaks in the envelope of low beta (12-15Hz) close to stimulus onset across all tempi. There was also modulation in the beta band at higher frequencies, but this was less consistent across all tempi. These results are generally in line with previous recordings of beta band activity from adults (Fujioka et al., 2012) and children (Cirelli et al. 2014, see also Chapter 11). Notably, similar results were obtained to (Cirelli et al., 2014) when using the same frequency ranges that they used (see Figure 10.5-10.7) .

It was found that typically developing children exhibit the beginning of a rebound in the envelope of beta band oscillations well before the onset of the sound. While this response peaks around 100ms after stimulus onset in each of the different tempos, the fact that it begins before the onset of the tone suggests it is predictive in nature. That children are able to predict the 585ms condition and the 780ms condition is consistent with the data reported by Cirelli et al. (2014). However, in contrast to their findings, additionally it is shown that children also exhibit a peak 80-100ms after the onset of the sound in the 390ms condition. The reason this study found significant differences between beta oscillations and zero likely relates to using a lower frequency range than Cirelli et al. (2014). As can be seen from Figure 10.5, the differences between beta oscillations and zero were generally only significant at an uncorrected threshold in the 20-25Hz frequency range. In contrast to this, in a

lower frequency range (12-15Hz), the results were mostly significant at a corrected threshold. This suggests it may be more appropriate to use a lower frequency range when examining neural responses associated with predicting the onset of the beat.

Another factor that could have contributed to us finding significant differences in the 390ms condition is that MEG allowed us to detect oscillations that were not picked up by EEG. While EEG is sensitive to both radial and tangential components, MEG is only sensitive to tangential components. It might be the case that MEG can reveal tangential sources that could be obscured by the contribution of the radial sources to the electrophysiological signal (see Cohen and Cuffin 1983).

Notably, there appeared to be some differences in the timing of the peaks and troughs of the beta band envelope compared to previous investigations of beta oscillations to isochronous stimuli. Whereas the beta band oscillations in the Fujioka et al. (2012) study tended to peak prior or within 100ms after stimulus onset, peaks in beta band activity in the current study occurred 100ms after stimulus onset. There are several possibilities that could account for this. One factor that could have contributed to the delayed peak in oscillatory activity is the experimental design. This study used a slightly different paradigm where the trains of rhythmic sounds were presented, that changed to a new tempo rather than staying constant throughout a single block. This would have increased uncertainty about the timing of the expected stimulus onset as the participants did not know when it would change and could have contributed to a delay in the peak of the beta band envelope. Additionally, the fact that shorter trains of sound (5-10 sounds) were used could might not have allowed for a fully predictive phase advance to occur (though see Todorovic et al. 2015). Nev-

ertheless, despite such differences, our results are still largely consistent with Cirelli et al. (2014). In the only other MEG study of isochronous beats in the beta band (Fujioka et al., 2012) beta power started to peak before stimulus onset and reached a maximum almost immediately after. In comparison, the responses appear to be slightly delayed. One possible reason for this is that the apparent delay is that I tested children rather than adults. Behavioural studies show that children as old as 10 years of age are less accurate in synchronising taps to an auditory beat than adults (Drake et al., 2000). This may be reflected in the corresponding neural mechanisms that support rhythm production and perception. Specifically, this immaturity could be manifested in a delay in the peak - rather than the relative power - of beta band activity.

While the experiment did not record neuromagnetic activity from adults and is therefore unable to make a direct comparison between two groups, our finding that children were able to track even the fastest tempo is intriguing. It could even be considered paradoxical: Why are children unable to produce rhythmic movements as well as adults if perception of rhythmic tones is adult like? The answer to this question may lie in the differences between perception and production of rhythms and the different demands that such tasks place on the brain. Although rhythm perception recruits motor areas of the brain (Bengtsson et al., 2009; Chen et al., 2008; Grahn et al., 2007) and rhythm production recruits auditory areas of the brain (Su and Pöppel, 2012), producing a rhythm is nevertheless quite different from perceiving it. For example, while passive listening, and listening with anticipation of tapping both recruit the supplementary motor area (SMA), the region is significantly more active during tapping than either of the listening conditions (Chen et al., 2008). Likewise,

the cerebellar lobule VI is engaged for both listening and tapping conditions, but shows a greater increase in BOLD response when tapping is anticipated or executed (Chen et al., 2008). Thus, while children are less accurate in synchronising movement to a beat than adults (Drake et al., 2000; Falk et al., 2014, 2015), it is possible that the neural mechanisms supporting rhythm perception are already established.

If the neural activity in the beta band is associated with rhythms and develops as a child ages, one might expect to find a significant correlation between these two measures. In line with this reasoning, a significant positive correlation was found between 585ms condition and age. This is intriguing given 585ms is the very close to the preferred tempo at which 8 year old children tap (588ms, see Drake et al. 2000). At the same time however, no significant correlation was recorded between age and the amplitude of maximal modulation of beta band oscillations in the other conditions. However it is important to consider the reasons why this might occur. One possibility is that too few subjects were used to reliability detect a correlation across all conditions. Indeed, previous work using MEG has already established a positive relationship between beta band oscillations and age (Gaetz et al., 2010). Another intriguing possibility is that the relationships between age and beta oscillations may emerge as a function of both age and preferred tempo. In theory, this could explain the observation of a significant positive correlation at the closest to optimum tempo (585ms) and a modest (though not significant) positive correlation between age and the 790ms condition, but not the 390ms condition. Such an idea however is speculative and remains to be verified by future research.

Is the finding that children exhibit neural responses that begin before the

onset of a sound consistent with accounts of human brain development? The human brain does not reach its full adult volume until about 12 years of age (Paus et al., 2001). Despite this, brain maturation is not yet complete. In particular, there are increases in grey matter in the superior temporal gyrus until about 16 years of age (Giedd et al., 1999). If children's brains are not yet mature, then they may have difficulty predicting the onset of sound at some tempi (as indexed a peak in beta band activity). This could be reflected in children being unable to track sounds in the 390ms condition as described by Cirelli et al. (2014). However, the results of our study did not fully support that the notion that children had difficulty tracking sounds at faster intervals. Instead, at lower frequencies (12-15Hz), I found that there was a peak in beta band activity close to the onset of the sound. This contention is supported by a work showing that babies are able to detect the omission of tones at a much faster (150ms) tempo (Winkler et al. 2009, see also 2 paragraphs below). Taken together, the data from the present experiment suggests that a child's brain may be able to process low-level features of sound in a similar fashion to adults. The most direct evidence for the similarity of the responses in adults and children comes from the fact that 7 month old infants can discriminate between different rhythms (Phillips-Silver and Trainor, 2005) and electrophysiological research showing that newborn infants are able to detect violation of rhythmic isochronous sounds (Winkler et al., 2009). A later study (Fujioka et al., 2011) showed that auditory specific rhythmic activity was evident in infants aged between 4 and 6 months of age. These studies demonstrate that capability to detect rhythmic sequences is already present at birth. From this perspective, it would be no surprise to find that children - even some young children - exhibit neural responses similar to adults. To the extent

that the perception of rhythm can be considered relatively simplistic, I assert that children do indeed exhibit an adult-like response to the perception of isochronous intervals.

However, just because children exhibit a beta band response that peaks close to the onset of stimulation does not mean they have established an internalised representation of the temporal interval. An internal representation of the tempo would also imply that a child exhibits a neuromagnetic response to a change in tempo. Previous work has shown that adults are readily able to detect changes in properties of auditory tones as indexed by a mismatch negativity response (for review see Näätänen et al. 2007). Most commonly this is observed in relation to frequency of tones (e.g. Näätänen et al. 1989) but has also be seen in relation to interstimulus interval (Ford and Hillyard 1981; Lai et al. 2011; Nordby et al. 1988; Takegata et al. 2001 and see also Kisley et al. 2004). Interestingly, Lai et al. (2011) found that in adults, shortening the temporal interval elicited a larger mismatch negativity response than did lengthening the interval between tones. Jongsma et al. (2007) suggested an earlier tone (i.e. a change to a shorter interval) would surprise the brain and evoke larger activity than would a later tone. The key question is: Are such responses evident in children?

Cheour et al. (1998), for example, found that the amplitude of the MMN response - the difference between frequent standard stimuli and infrequent deviant stimuli - is similar to that of adults. However, they also showed that the latency of the MMN response decreased with increasing age. More recent evidence suggests that newborn infants (1-3) days old are able to detect both changes in the tempo

of an isochronous sequence as evidenced by evoked electrophysiological responses (Háden et al., 2015). This is in line with previous research examining auditory evoked potentials to changes in tempo in infants (Brannon et al., 2008; Otte et al., 2013). Otte et al. (2013) presented 2 month old infants with a trains of sounds with an interstimulus interval of 300ms that was occasionally shortened to 100ms. This led to a mismatch response that peaked between 215 and 235ms after the deviant interval. Brannon et al. (2008) examined how the ratio of shorter deviant ISI to the longer standard ISI affected the MMN response in 10 month old infants. They reported that the MMN response in infants was similar to that in adults and exhibited increasing amplitude with a greater disparity between the standard and deviant ISI's. More recently, this has been observed in newborn infants 1-3 days old using intervals of 150ms and 50ms (Háden et al., 2015). These authors showed that infants exhibit a larger MMN response to shortening intervals relative to lengthening intervals. Thus the ability to detect changes in tempo is also evident at a very young age.

The current study extends previous work by showing that typically developing children exhibit a neuromagnetic mismatch response to an unpredictable slowing of tempo. Specifically, greater evoked activity was found in the right hemisphere between 200-300ms when comparing the mismatch response (the difference between the response to a change in tempo to the interval that is being changed to) compared to zero. A similar but less prominent response was seen in the left hemisphere. Importantly, the data reported here is consistent with the findings of Háden et al. (2015) who showed a mismatch response at 249ms in newborns and Otte et al. (2013) who found a mismatch response between 215 and 240ms. The fact that children exhibit a

mismatch response to an unpredictable change in tempo provides additional evidence that they have established an internal representation of the temporal interval.

Finally, this study shows that it is indeed possible to measure evoked responses and rhythmic entrainment envelope of neural oscillations from young children using MEG. Researchers investigating children have tended to use EEG in favour of MEG due to the latter being much less tolerant of movement and generally not suitable for children because of the adult sized fixed sensor geometry. However, it appears that some children are able to remain still for the extended period of time required to conduct the experiment . Thus, our paper paves the way for future work to consider the use of MEG to investigate the spatial and temporal dynamics of rhythm perception in young children. This is an exciting prospect in the context of developmental disorders because it is well established that rhythmic stimuli can aid fluency in people with speech disorders (e.g. Toyomura et al. 2011, 2015). I speculate that that regular external stimulation may aid the fluent production of speech by modulating beta power in such a way that children with speech disorders are better predict the moment at which to initiate syllables.

10.5 Limitations and Conclusion

The study was limited because unlike the Cirelli et al. (2014) paper, no direct comparison was made between adults and children. Despite this, the pattern of beta band modulation found in this study very closely resembles the responses previously observed in adults (Fujioka et al. 2012 and see also Figure 10.6-10.7). Despite the relatively small number of trials in the change conditions in the evoked response,

effects at a strict statistical threshold were still found. However, the possibility that there were actually differences between the lengthening conditions cannot be ruled out as the small number of trials may have been insufficient to elicit differences in beta band oscillations. Finally, the current study had no direct behavioural measure of rhythmic ability and are therefore unable to link it with beta band dynamics.

This is the first study to measure neuromagnetic beta band oscillations to isochronous sounds in typically developing children. Children exhibit similar patterns of beta band oscillations to adults in response to isochronous tones. This response likely occurs in a slightly lower frequency band than first thought. This research should encourage others to investigate the neural mechanisms that support rhythm perception in children. Future studies can focus on investigating the perception of rhythm in children with developmental disorders such as stuttering.

Chapter 11

Abnormal Time Course of Low Beta Modulation in Non-Fluent Preschool Children: A Magnetoencephalographic Study of Rhythm Tracking

A version of this chapter has been submitted for publication in a peer reviewed journal (NeuroImage) and is being revised in response to comments from anonymous reviewers

11.1 Introduction

Stuttering is a neurodevelopmental disorder characterised by speech dysfluencies in the form of repetitions, prolongations and blocks (World Health organisation, 2010). It has a peak onset age of 3-5 years. It is estimated that anywhere from 32% (Johnson et al., 1959) to 80% (Yairi and Ambrose, 1999) of the children who begin to stutter will spontaneously recover, while the rest will continue to stutter into adulthood. In the last century, significant resources have been devoted to elucidating the cause of stuttering and numerous explanations have been proposed. It has been suggested that stuttering results from dryness of the tongue, adverse parental reactions to normal childhood dysfluencies or that it is a psychogenic disorder (for review see Büchel and Sommer, 2004). None of these explanations have received overwhelming support. More recently, investigations have shifted focus to compare patterns of brain activity in PWS and PWDS. These studies have documented an array of anomalies in the structure and function of both cortical and subcortical regions in stuttering and have produced a variety of explanations regarding the brain basis of stuttering (see Brown et al. 2005; Belyk et al. 2015; Budde et al. 2014, for review). Investigations into the neurological underpinnings of stuttering via electrophysiological and brain-imaging studies may bring us closer to understanding its cause.

A great deal of progress has been made in elucidating differences in brain structure and function activity between PWS and PWDS. For example, there are significant differences in the haemodynamic response in auditory and motor regions when speaking (Toyomura et al., 2011) at rest (Xuan et al., 2012) and in the structural connectivity between auditory and motor areas (Cai et al., 2014b) and between

motor regions (Kronfeld-Duenias et al., 2014) of the brain. Despite this, there remains significant uncertainty about the cause of the disorder. This is partly because most studies have focused on adults, making it hard to determine whether the observations of structural and functional anomalies are causally related to stuttering or the result of compensatory neuroplastic reorganisation (Chang and Zhu, 2013; Etchell et al., 2014a,b). Unlike AWS who have adapted to stuttering over time, such compensatory neural reorganisation is not generally found in CWS (Chang et al., 2008; Chang and Zhu, 2013; Beal et al., 2013). Studies of CWS are therefore crucial for isolating the neural origin or source of dysfluency. However, researchers face considerable difficulties in studying young children because of their inability to maintain sustained attention for the length of time necessary for the successful completion of even behavioural experiments. Recording neural activity during such experiments adds a further layer of complexity. For because neuroimaging studies place significant demands on young children by requiring them to remain as still as possible for extended periods of time, or are conducted in an environment that is noisy or confined and not well tolerated by this population, the majority have focused on AWS. Notably however, a number of studies have examined the brains of CWS (see Chang et al., 2015; Sato et al., 2011; Sowman et al., 2014). These methodological challenges perhaps explain why there are so few behavioural or neuroimaging studies of CWS.

Studies examining the behavioural performance of CWS provide valuable insight as to what might be causing the disorder. By and large they converge on the idea that stuttering is a disorder associated with temporal processing (see Etchell et al., 2014b, for a review). For example, Olander et al. (2010) found that the

variability of paced and unpaced clapping in CWS was significantly greater than in CWDS and that this variability was bimodally distributed. Specifically, the variability of 60% of the CWS overlapped with the variability of the CWDS, but 40% of the CWS exhibited variability that was worse than the poorest performing CWDS. Interestingly, these numbers closely corresponded to the number of children aged 4-6 years old (65%) who generally recover from stuttering (Yairi and Ambrose, 1992) and those who do not. The researchers took their findings to suggest that timing performance (as defined by the ability to clap to a beat) amongst that cohort was predictive of recovery from stuttering. It could be argued that a time processing disorder is potentially a cause of stuttering. Falk et al. (2014) compared the behavioural performance of children and adolescents who did and did not stutter in synchronising finger taps to simple and complex musical beats. At various inter-stimulus rates (450, 600ms and 750ms) CWS exhibited poorer behavioural performance (both in accuracy and variability) as compared to CWDS. Whereas the performance of CWDS improved with age, the performance of CWS did not. Furthermore, the analysis of behavioural performance revealed that low synchronisation accuracy was associated with increased stuttering severity, leading the authors to conclude that developmental stuttering could be linked with a more generalised deficit in timing (Falk et al., 2014).

11.1.1 Neuroimaging studies of CWS

One current neurophysiological explanation for stuttering is that it is a disorder of the internal timing network (comprised of the basal ganglia and the supplementary

motor area) and that these temporal processing deficits can be compensated for by an external timing network [comprised of the cerebellum, premotor cortex and right inferior frontal gyrus]. This explanation derives from the fact that there is a great degree of overlap in the neural structures underpinning rhythmic timing and speech production/perception (see Fujii and Wan, 2014). This contention is further supported by a host of neuroimaging studies linking deficits in this network to stuttering. For example, Beal et al. (2013) used structural MRI to compare grey and white matter volumes between CWS and CWDS. They found decreased grey matter volume in the left putamen of CWS which they suggested was particularly interesting in light of emerging evidence for difficulties in speech motor sequence learning in PWS and the recognised role of the left putamen in motor sequence learning (Beal et al., 2013). Beal et al. (2013) concluded that abnormalities in the neurodevelopmental trajectory of regions such as the left putamen, bilateral inferior frontal gyrus and supplementary and premotor cortex may result in the breakdown of accurate speech motor learning and control. Similarly, Chang and Zhu (2013) examined functional resting state activity and used DTI to investigate differences in the structural connections of the brains of CWS and CWDS. The authors found attenuated functional activity (as measured by correlations between the left putamen and the right posterior superior temporal gyrus, left SMA and left insula) and structural connectivity (between the left putamen and the left inferior frontal gyrus and the middle temporal gyrus as measured by white matter tractography) in CWS as compared to CWDS. Chang and Zhu (2013) concluded that CWS have attenuated connectivity in neural networks that support timing of self-paced movement control. The young participants were included in Chang and Zhu's study very soon after the

onset of their stuttering symptoms. Hence, it is likely that subcortical regions like the putamen are causally related to the onset of stuttering. While there are relatively well-established abnormalities in the structure and function of cortical regions in stuttering, far fewer studies have examined whether there might be abnormalities in oscillatory neural dynamics within these cortical regions and whether or not such differences can be related to putative temporal processing deficits in stuttering.

11.1.2 Neural Oscillations and Timing

Neural oscillations refer to rhythmic fluctuations in the excitation and inhibition of large populations of neurons that can be recorded using tools like MEG or EEG and are most probably caused by changes in large scale synchronous transmembrane currents (Thut et al., 2012). These oscillations are characterised according to the frequency at which they occur and can each be linked to different cognitive functions. For example, the delta band is prevalent during the sleep cycle and the gamma band is associated with memory. The beta band is modulated prior to and during the execution, observation and imagination of movement (Burianová et al., 2013, 2014; Kilavik et al., 2013). Specifically, beta band activity drops (desynchronises) immediately prior to and during movement before increasing (resynchronising) once the movement becomes stable. There are many theories about the function of neural oscillations in the brain. One such theory posits that the function of oscillatory activity is to predictively focus attention at salient events by (for example), entraining the brain to auditory stimuli (Large and Jones, 1999). According to this view, neural oscillations are crucial for processing temporal information because of their inherent

regularity (Arnal and Giraud, 2012; Zanto et al., 2006; Fujioka et al., 2009). A less well known characteristic of the beta band is that it may be particularly important for temporal processing. Recent data indicates that passively listening to isochronous sounds modulates beta band activity in the auditory cortices at the rate of the pacing stimulus (Fujioka et al., 2012). In the Fujioka et al. (2012) study, participants passively listened to trains of isochronous sounds of either 390, 585 or 780ms, or to sounds whose period varied randomly between 390 and 780ms. Time-frequency analysis of auditory cortex virtual sensor data derived from MEG recordings revealed a decrease in beta band power 200ms after stimulus onset that was identical across both the rhythmic and random conditions. However, the rising slope of the beta band activity (also known as the beta rebound) was modulated according to the rate of isochrony. Whereas the beta rebound peaked before the next expected stimulus in the rhythmic condition, in the random condition, the rebound was much less steep. Based on these data, the authors suggest that beta rebound may be a neural mechanism for predictive timing. More recently, Cirelli et al. (2014) replicated the Fujioka et al. (2012) study paradigm in an EEG experiment on children. Cirelli and colleagues demonstrated that children as young as 7 years of age exhibit a similar pattern of activity to adults for the slower, but not faster tempos in the auditory cortex. This finding demonstrates that typically developing school-aged children and adults exhibit comparable beta band responses to rhythmic and less rhythmic sounds.

11.1.3 Neural Oscillations Stuttering

Only four published reports exist that describe beta band dynamics in PWS, and none have examined them in the context of temporal processing. Rastatter et al. (1998) investigated the effects of delayed auditory feedback on oscillatory activity of adults who stuttered. The authors showed that this fluency-inducing technique markedly reduced hyperactivity of the beta band in adults who stuttered relative to a baseline resting condition. Salmelin et al. (2000) used MEG to compare the sequences of cortical beta band activation during single word reading in stuttering and non-stuttering adults. While the overt behavioural performance of the two groups was identical, there were marked differences in the sequence of beta band responses. In contrast to the AWDS, the AWS had significantly weaker beta band modulation in the hand and mouth areas of the motor cortex during speech production. Additionally, while the fluent adults displayed salient time-locked responses in the mouth area of the motor cortex, no such response was evident in the AWS, suggesting that whilst the rolandic operculum was active, the responses in this region were not properly synchronised. A later study by Özge et al. (2004) found that children who stutter exhibit hypoactive beta band oscillations at rest. Most recently, Joos et al. (2014) recorded functional resting state activity using EEG in groups of AWS and AWDS. They found that while there were no differences in the magnitude of neural activity, AWS had decreased connectivity in the low beta band (12-18 Hz) between inferior frontal, motor and premotor regions (as measured by coherence). Interestingly, these differences were positively correlated with the impact of stuttering on every day life, suggesting that abnormalities in the low beta band are functionally associated with

stuttering. Moreover, low beta band - and not high beta band activity - is sensitive to dopamine modulation (Friston et al., 2015) and dopamine can also modulate stuttering (see for review Brady et al. 1991; see also Alm 2004). Based on evidence from studies examining the beta band in stuttering as well as those investigating the structure and function of the basal ganglia in AWS and CWS, it has been suggested that striatal abnormalities are reflected in abnormal beta oscillations (Etchell et al., 2014b). Unfortunately this contention is difficult to verify because it is not routinely possible to make electrophysiological recordings from the striatum in humans. Nevertheless, since there is a relationship between cortical and subcortical beta band activity (Jenkinson et al., 2013) it might be possible to detect differences, should they exist, in cortical beta band activity in response to rhythmic sounds in PWS. Given that stuttering most commonly emerges in the preschool years, observation of abnormal beta band entrainment to rhythmic sounds would support the claim that stuttering is a disorder of temporal processing. The present experiment was designed to test the hypothesis that beta band entrainment by rhythmic sounds is abnormal in CWS.

11.2 Method

11.2.1 Participants

10 stuttering children (aged 3 to 9 years, 7 male 3 female) and 10 aged-matched controls (3 to 9 years, 6 male, 4 female) participated in this study. Stuttering participants were recruited through advertisements in local papers. None of the control

participants reported any history of speech, language or hearing difficulties. Normal hearing thresholds between 500Hz and 2000Hz were confirmed with audiometric testing (Symphony (software), Amplitude T3 Series (hardware) Otovation, PA). Prior to inclusion in the study children in both groups were screened for age appropriate language development by means of the Preschool Language Screener (PLS-4, I. L. Zimmerman et al. 2002) or the Clinical Evaluation of Language Fundamentals (CELF-P2; Semel et al. 2006). Parents or guardians provided written informed consent for their child's participation. The criteria for inclusion in the study was a 'passing' score on each of the subscales of the PLS or the CELF depending on which was administered. This was taken to reflect normal language skills for children of that age. This study was approved by the Macquarie University Human Research Ethics Committee (see Appendix E for final approval).

11.2.2 Fluency Assessment

CWS were diagnosed by an independent speech pathologist. Stuttering severity on the day of the recording was assessed by means of recording a 10-minute conversation with each child which was subsequently analysed for percentage syllables stuttered by a second independent trained speech pathologist. Other relevant details such as handedness, age of onset, gender, and severity of stuttering are summarised in Table 11.1.

Table 11.1: Demographic characteristics of participants: % SS or SR (italics) when assessed for speech therapy refers to the percentage of stuttered syllables/the severity rating (on a scale from 1-10 where 1 is no stuttering and 10 is the worst stuttering imaginable) when first assessed for speech therapy (i.e. upon diagnosis by a speech pathologist). %SS/SR (italics) at data collection refers to the percentage of syllables stuttered as assessed by a speech pathologist based on a 10 minute voice sample recorded on the day of the experiment. The Parent assessed SR at data collection, the SR at least fluent stage and the Present SR respectively refer to the parental rating of stuttering severity on the date of testing, when the child is least fluent and several months after the child participated in the experiment.

Participant Demographics									
							Stuttering Subjects	*Non Stuttering Subjects*	
Number							n=10	n=10	
Male Female							7-3	6-4	
Mean Chronological Age (Years, Months, SD)							5y 4m ± 22m	5y 10m ± 22m	
ID	**Gender**	**Handedness**	**Age of Onset of Stuttering**	**SR at least fluent stage**	**% SS or SR when assessed for speech therapy**	**% SS at data collection**	**Parent assessed % SR at data collection**	**Present SR**	**Treatment**
S1	M	R	3y 0m	6	5.6	12.3	3	1-3	Y Current
S2	F	R	2y 0m	9	14	2.4	2	1-3	N
S3	M	R	3y 0m	9	8.3	4	5	2-4	Y Completed
S4	M	L	3y 0m	6	4	0	2	1-3	Y Completed
S5	M	R	3y 6m	6	2.1	5.8	5	2	Y Completed
S6	F	R	2y 10m	8	10.3	0.3	7-8	1	Y Completed
S7	M	R	1y 10m	8	12.6	6.7	5	2-3	Y Current
S8	F	R	2y 7m	6	4	3.6	4	1-2	Y Completed
S9	M	L	2y 5m	8	18.1	10.4	4	1-7	Y Completed
S10	M	R	2y 0m	3	3.1	0	2-3	2	Y Current

11.2.3 Stimuli

Auditory stimuli were 50ms 2000-3000Hz broadband sounds created in Audacity 2.00 ($http://audacity.sourceforge.net/$). High frequency sounds were used because pilot testing found there were occasions when using more conventional stimuli (e.g. 1000Hz) did not play reliably or were reported to be uncomfortable by some participants. There were two experimental conditions. In the rhythmic condition, participants were presented with sounds with a stimulus onset asynchrony (SOA) of 450ms (equivalent to a stimulus rate of 2.2Hz). In the 'less rhythmic' condition, participants were presented with sounds with an SOA that randomly varied from 300-600ms (in increments of 20ms i.e. 300ms, 320ms, 340ms etc.), with an average SOA of 450ms (equivalent to a mean stimulus rate of 2.2Hz). The rationale for using an SOA of 450ms was based on the finding that it approximately corresponds to the spontaneous motor tempo for 2 and 4 year old children (Provasi and Bobin-Bègue, 2003) when they are asked to tap at their most comfortable rate, and to synchronise their taps with a 400ms, 600ms or 800ms metronome. Additionally, this rate was also used to assess the rhythmic production abilities of AWS and AWDS

11.2.4 MEG recording

Neuromagnetic responses were recorded using three different MEG systems. The first system was a custom built paediatric MEG (Model PQ1064R-N2, KIT, Kanazawa, Japan) consisted of 64 coaxial first order gradiometers with a 50mm baseline (Kado et al., 1999; Uehara et al., 2003). During the process of data collection, this system was upgraded and fitted with 112 coaxial first order gradiometers: this constituted

the second system. The third system was an adult-sized MEG (Model PQ1160R-N2, KIT, Kanazawa, Japan) containing 160 coaxial first order gradiometers used to record activity of those children whose heads did not fit in the paediatric system. 8 CWDS and 3 CWS were tested in the original child (64 channel) system; 2 CWDS and 5 CWS were tested in the upgraded child (112 channel) system and 2 CWS were tested in the adult (160 channel) system. Notably, each of the three systems were contained within the same magnetically shielded room and therefore environmental noise across the three systems was constant. Prior to MEG measurements, five marker coils were placed on an elasticised cap on the participant's head and their positions and the participant's head shape were measured with a pen digitizer (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing marker coils in the MEG dewar both before and after the recording session. Participants with movement exceeding 5mm were excluded from further analysis. In this manner, one participant was rejected. During recording, participants lay supine with their arms by their sides whilst watching a silent movie of their choice. Additionally, to ensure the younger participants were comfortable, a researcher sat with them at all times throughout the experiment. This also served to ensure the participants did not move during the experiment or synchronise/syncopate movement with the beats. This was further confirmed by online monitoring of the child by video camera from outside the magnetically shielded room for the duration of the experiment by a second researcher.

11.2.5 Data Analysis

All data were analysed using SPM (Wellcome Institute, London, UK) running on Matlab R2012a (The MathsWorks, Natrick, USA). The raw data was sampled at 1000Hz. Using the fieldtrip visual artefact rejection toolbox (which expresses every time point as a deviation from the mean over all time and channels), trials were rejected with a Z value >2. In this manner, no more than 5% of the total number of trials or the total number of trials for each condition was rejected. Continuous raw data was down-sampled to 250Hz and band-pass filtered from 1 to 40Hz. The MEG epoch extracted for analysis was -800 ms to 1100 ms after the tone onset (identical to Fujioka et al., 2012). Since activity was recorded using three different MEG systems, I needed to standardise the number and position of the sensors across our subjects. To do so, the sensors were realigned from each subject's recordings into a standardised space containing 64 sensors using the 'ft_megrealign' script implemented in the FieldTrip toolbox (Fieldtrip Toolbox for MEG/EEG Analysis; F. C. Donders Centre, Radboud University Nijmegen, Nijmegen, The Netherlands). Briefly, this procedure interpolates MEG signals onto standard gradiometer locations by projecting individual time-locked data to a coarse source reconstruction. The realignment is achieved by calculating a minimum norm estimation using a large number of dipoles placed in the upper layer of the brain surface (approximately 2.0 from the scalp) followed by a forward computation towards the template gradiometer array. The resulting signals are then recalculated to match standard gradiometer locations. An added benefit of this procedure is that it also corrects for head location across individuals. Importantly, such a procedure is proven to be robust and yields accurate results

even when there are substantial differences in the locations of the original and standardised sensor locations (Knösche, 2002). Although the Knosche algorithm script was not originally developed to remove noise from different systems, the implementation of this in 'ft_megrealign' has been demonstrated to be applicable to changing between systems with different numbers and/or positions of sensors. For an example of how to interpolate sensors from different systems, the reader is referred to the website $http://www.fieldtriptoolbox.org/example/megrealign$. The resulting channels were then relabelled according to the conventions of the 64 sensor system. Since I was primarily interested in auditory motor activity, for each subject an array of sixteen sensors were selected over the fronto-temporal regions of the scalp bilaterally, avoiding selection of midline, and occipital channels (see Figure 11.1). The analysis was conducted in sensor space rather than source space because the study was focused on determining whether or not there was a difference in beta modulation between CWS and CWDS rather than precisely where that difference was located in the brain. Additionally, because it was a novel experiment, I wanted to remain as close as possible to the original data and not to make assumptions about the potential source of the differences.

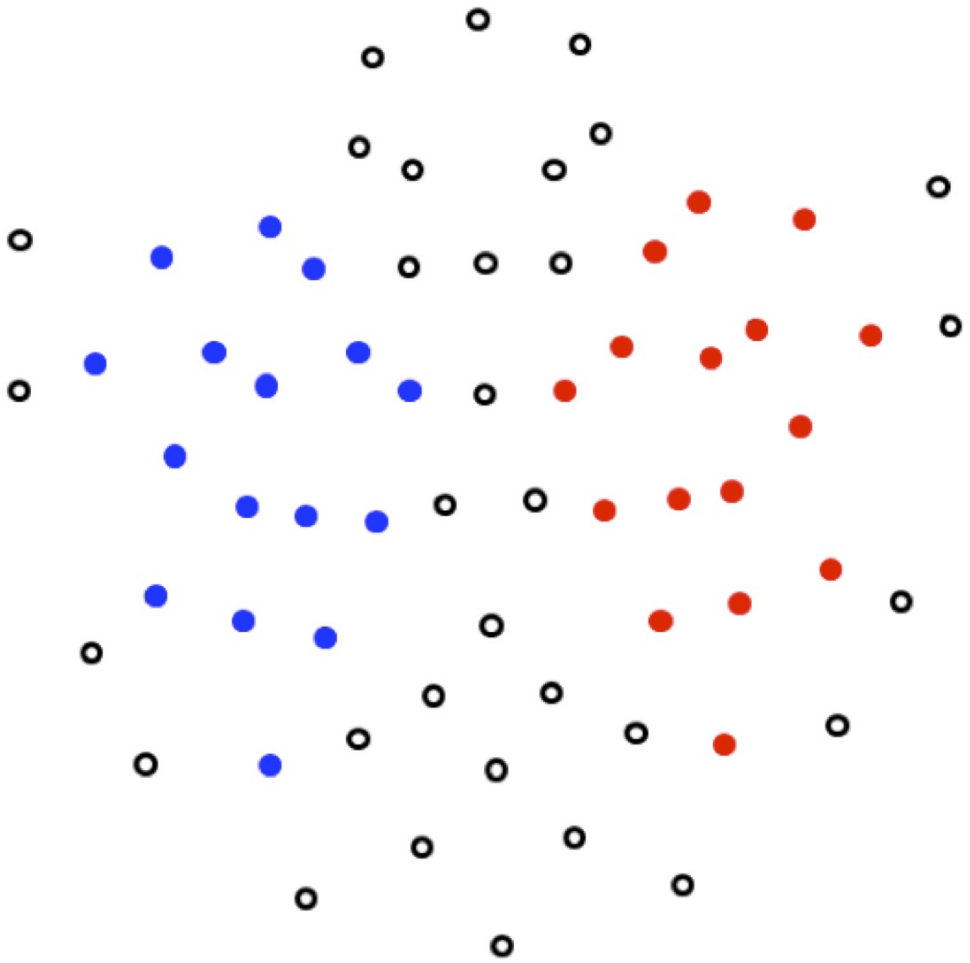

Figure 11.1: Array of sensors selected for analysis for each subject. The solid blue and red dots depict the 16 sensors representative of the left and right hemisphere respectively. The open black dots depict the remaining 32 sensors that were not analysed. The sensors depicted here are overlayed on the head position of a representative subject. The top of the image is anterior to the head and the bottom of the image is posterior to the head. Left is on the left and right is on the right.

Time-frequency decompositions were calculated separately for each individual and stimulus condition from 1-40Hz using a Morlet wavelet transform (Bertrand et al., 1994) and averaged across trials. The averaged plots were then cropped in the time domain from -500 to 800ms so as to reduce artefacts occurring at the edge of the spectrogram. The plots were then rescaled relative to the mean of the entire epoch for each frequency bin. This resulted in the relative power being expressed as a

percentage change of the mean power within a frequency bin across the whole epoch. Each individual thus had time frequency data for two hemispheres, each containing sixteen sensors. The average of the 16 time-frequency transformed sensors was then computed for each subject resulting in two time frequency matrices per subject (one for each hemisphere). Using these matrices, I then calculated the grand average of the left and right hemispheres within each group (plotted in Figures 11.2 and 11.3). For statistical analysis, and to illustrate the change in beta power across conditions, I collapsed across a 12-15 Hz frequency window in the low beta band where modulation was maximal. The decision to examine the beta band envelope was made a priori and was based on Fujioka et al. (2012) and Cirelli et al. (2014). Differences were expected between CWS and CWDS to be evident in the low beta band (approximately 12-18Hz) due to one study showing differences in coherence between brain areas in AWS and AWDS (Joos et al., 2014). The decision to examine the specific range of 12-15Hz was made post hoc. The justification for selecting this particular frequency band is twofold. Firstly, beta modulation was found to be greatest in the 12-15Hz range (as opposed to higher frequency ranges see Chapter 10). The second reason for using a lower range is to avoid bias in the response to a particular group or condition (which could happen if selected on an a priori basis). Visual inspection of the data revealed that this range appeared to be the least bias across the CWS and the CWDS. A non-parametric ANOVA was conducted with factors of group (controls vs. stutterers) and hemisphere (left vs. right) implemented using the 'std_stat' function of the EEGlab toolbox (Delorme et al., 2006) for the epoch 0-450ms (the time for which there was no overlap between stimuli). The nonparametric ANOVA compared the intensity of the time frequency response and tested for interactions across every time point. A

total of 100,000 permutations were run and set statistical significance at a p-value of 0.05, false discovery rate (FDR) corrected. This analysis was run separately for the rhythmic and less-rhythmic conditions. At the request of an anonymous reviewer, the same methods were used to analyse the data in the 15-30Hz range - I refer to this as the high beta band in order to differentiate it from the 12-15Hz low beta band in this study.

11.3 Results

Time-frequency analysis showed there was modulation of the low beta band (12-15Hz) in both the regular and the random condition for both groups of participants that tracked the mean rate of stimulation (see Figures 11.2 and 11.3). The leftmost panels of Figure 11.2 depict the entire time-frequency range for the rhythmic condition. The right two panels depict the grand average data that has been collapsed across frequency in the low beta (12-15Hz) band for the rhythmic condition. Similarly, the left two panels of Figure 11.3 depict the entire time-frequency range for the less rhythmic condition. The right two panels depict the grand average data that has been collapsed across frequency in the low beta (12-15Hz) for the less rhythmic condition. Visual inspection of the left and right hemispheres (Figures 11.2 and 11.3) revealed a similar pattern of beta band modulation between the left and right hemispheres across the entire epoch. This observation was confirmed by the results of our statistical analysis. The interaction of group (control vs. stutterers) and condition (left hemisphere vs. right hemisphere) was not significant. There was however, a main effect of group (stutterers vs. non stutterers). Figure 11.4 and 11.5 depict a

comparison of the beta band envelope for CWDS and CWS in the rhythmic and less rhythmic condition. Significant differences in the envelope of the beta band between groups are highlighted in grey. Note that the final plots (Figures 11.4 and 11.5) represent activity from a total of 32 sensors (16 from each hemisphere). Interestingly, this analysis revealed an apparent 180 degree phase shift in the envelope of the 12-15Hz oscillations between the CWS and the CWDS. The results of the 'high beta' band analysis revealed no significant differences between CWS and CWDS in the rhythmic condition, but did show a difference in the less rhythmic condition.

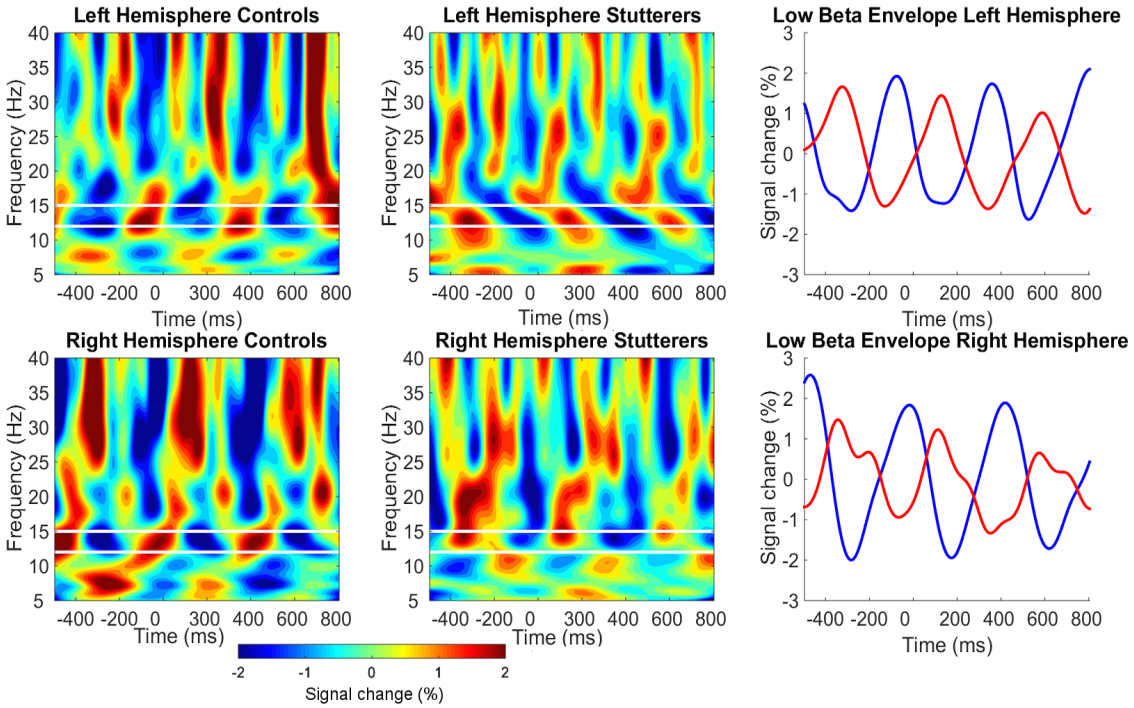

Figure 11.2: Time Frequency Decompositions for 12-15Hz in the rhythmic condition. The left two columns show time frequency plots from 12-15Hz and -500 to 800ms peristimulus time. The white horizontal lines depict 12-15Hz range over which the beta band was collapsed for statistical analysis. The signal change percentage represents the percentage change from the mean of the entire epoch. The rightmost plot depicts the intensity of the beta band envelope as a percentage change from the mean of the entire epoch (collapsed across the 12-15Hz range) to rhythmic stimuli for the control subjects (blue) and the stuttering subjects (red) in the left (top) and right (bottom) hemisphere respectively N=10.

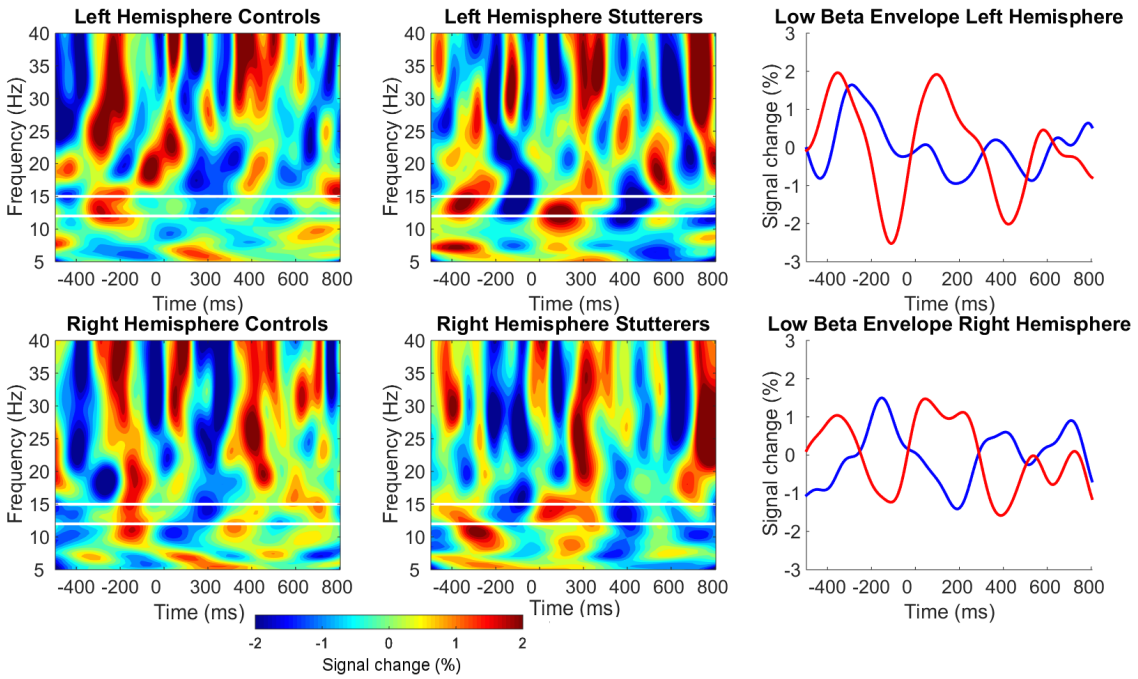

Figure 11.3: Time Frequency Decompositions for 12-15Hz in the less rhythmic condition. The left two columns show time frequency plots from 12-15Hz and -500 to 800ms peristimulus time. The white horizontal lines depict 12-15Hz range over which the beta band was collapsed for statistical analysis. The signal change percentage represents the percentage change from the mean of the entire epoch. The rightmost plot depicts the intensity of the beta band envelope as a percentage change from the mean of the entire epoch (collapsed across the 12-15Hz range) to less rhythmic stimuli for the control subjects (blue) and the stuttering subjects (red) in the left (top) and right (bottom) hemisphere respectively N=10.

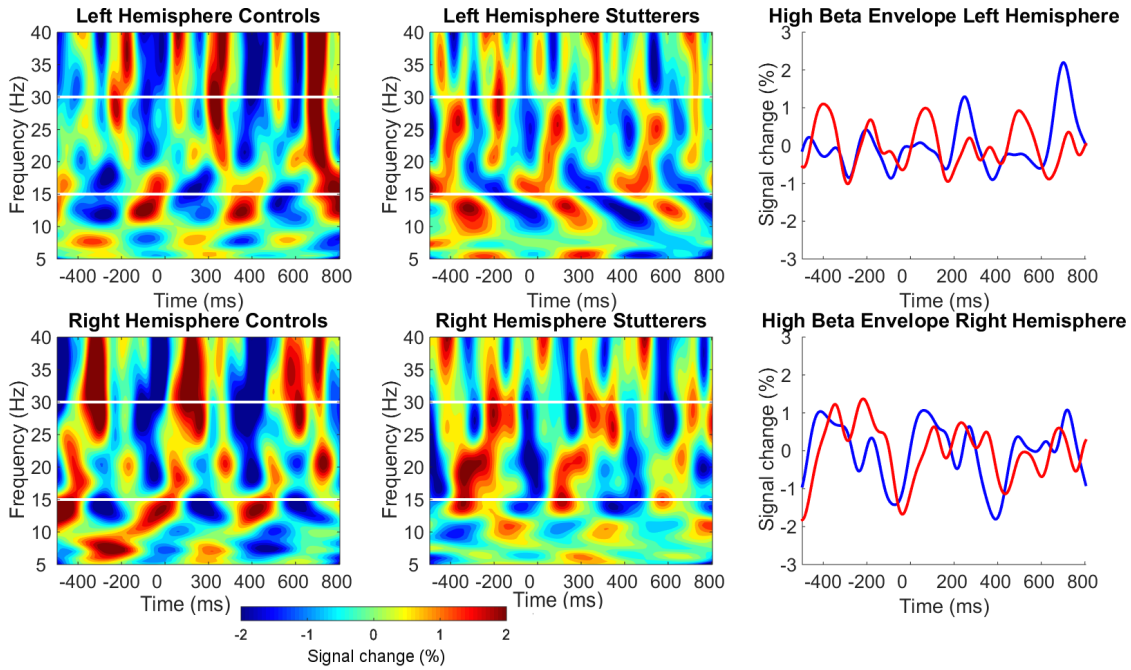

Figure 11.4: Time Frequency Decompositions for 15-30Hz in the rhythmic condition. The left two columns show time frequency plots from 15-30Hz and -500 to 800ms peristimulus time. The white horizontal lines depict 15-30Hz range over which range over which the beta band was collapsed for statistical analysis. The signal change percentage represents the percentage change from the mean of the entire epoch. The rightmost plot depicts the intensity of the beta band envelope as a percentage change from the mean of the entire epoch (collapsed across the 15-30Hz range) to rhythmic stimuli for the control subjects (blue) and the stuttering subjects (red) in the left (top) and right (bottom) hemisphere respectively N=10.

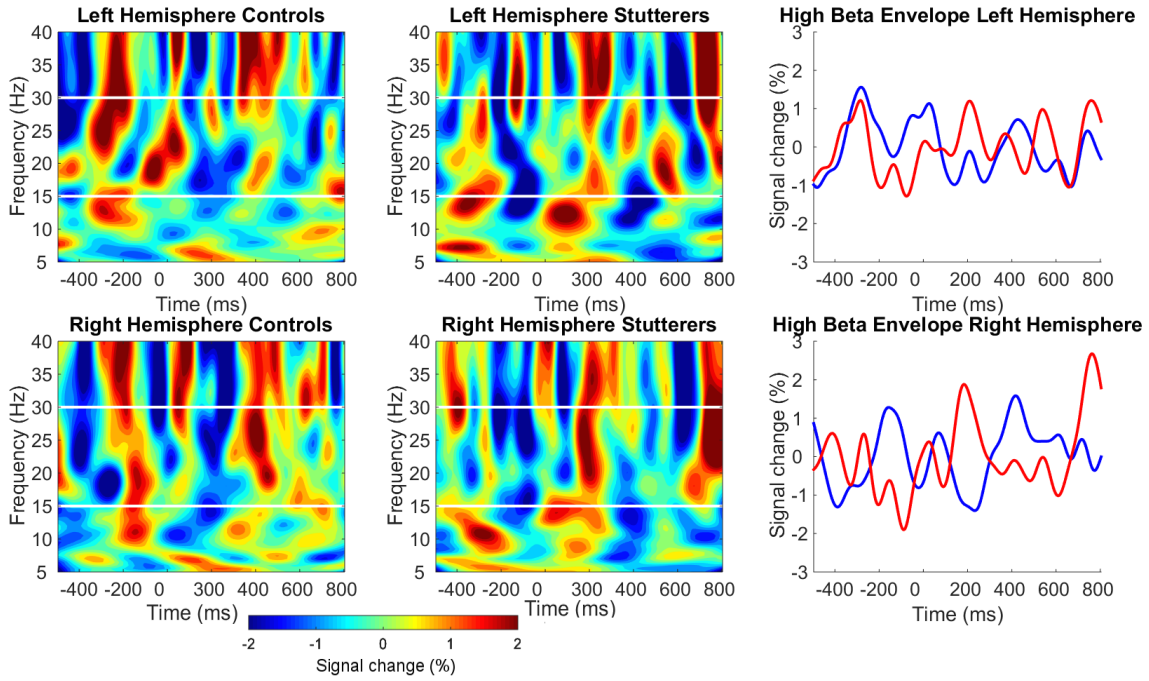

Figure 11.5: Time Frequency Decompositions for 15-30Hz in the rhythmic condition. The left two columns show time frequency plots from 15-30Hz and -500 to 800ms peristimulus time. The white horizontal lines depict 15-30Hz range over which range over which the beta band was collapsed for statistical analysis. The signal change percentage represents the percentage change from the mean of the entire epoch. The rightmost plot depicts the intensity of the beta band envelope as a percentage change from the mean of the entire epoch (collapsed across the 15-30Hz range) to rhythmic stimuli for the control subjects (blue) and the stuttering subjects (red) in the left (top) and right (bottom) hemisphere respectively N=10.

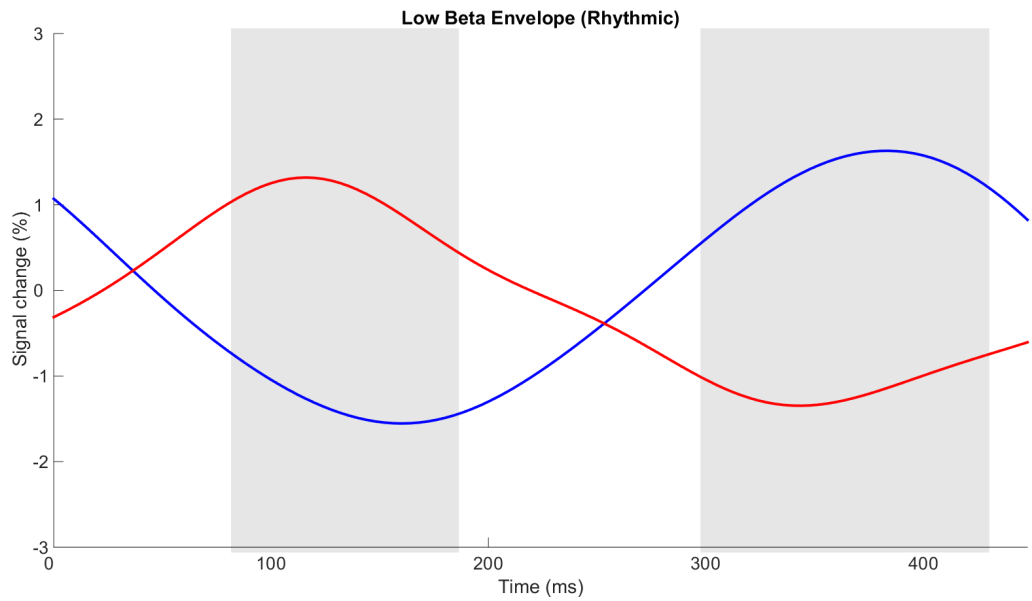

Figure 11.6: Time Frequency responses for the rhythmic condition. The plot depicts the percentage change of time frequency responses from the mean of the entire epoch for the control subjects (blue) against the stuttering subjects (red) from 0ms to 450ms relative to the onset of the tone. The grey areas depict time points at which there is a significant difference between groups (p=0.05 FDR corrected). N=10.

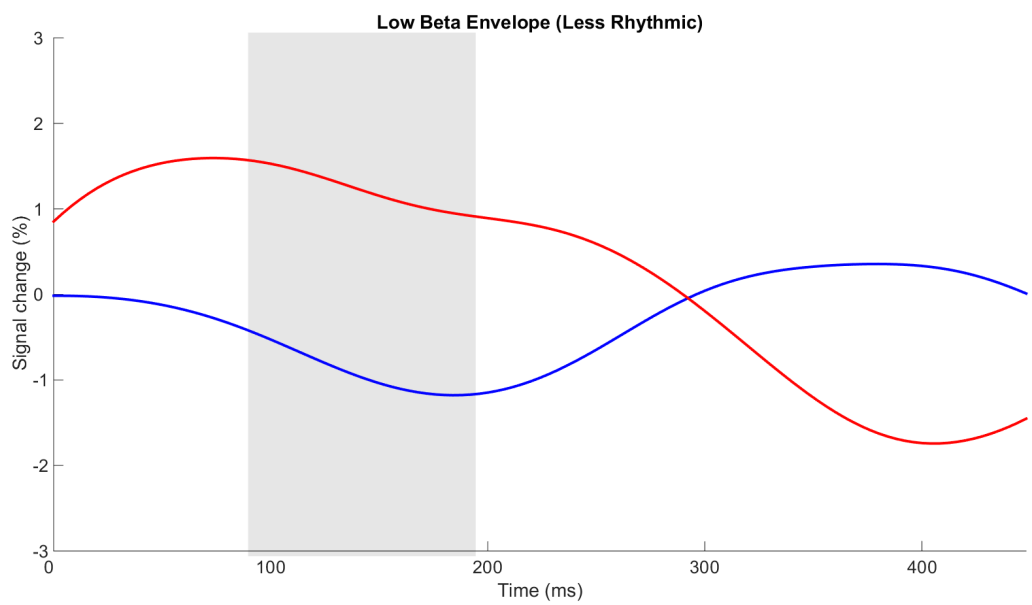

Figure 11.7: Time Frequency responses for the less rhythmic condition. The plot depicts the percentage change of time frequency responses from the mean of the entire epoch for the control subjects (blue) against the stuttering subjects (red) from 0ms to 450ms relative to the onset of the tone. The grey areas depict time points at which there is a significant difference between groups (p=0.05 FDR corrected). N=10.

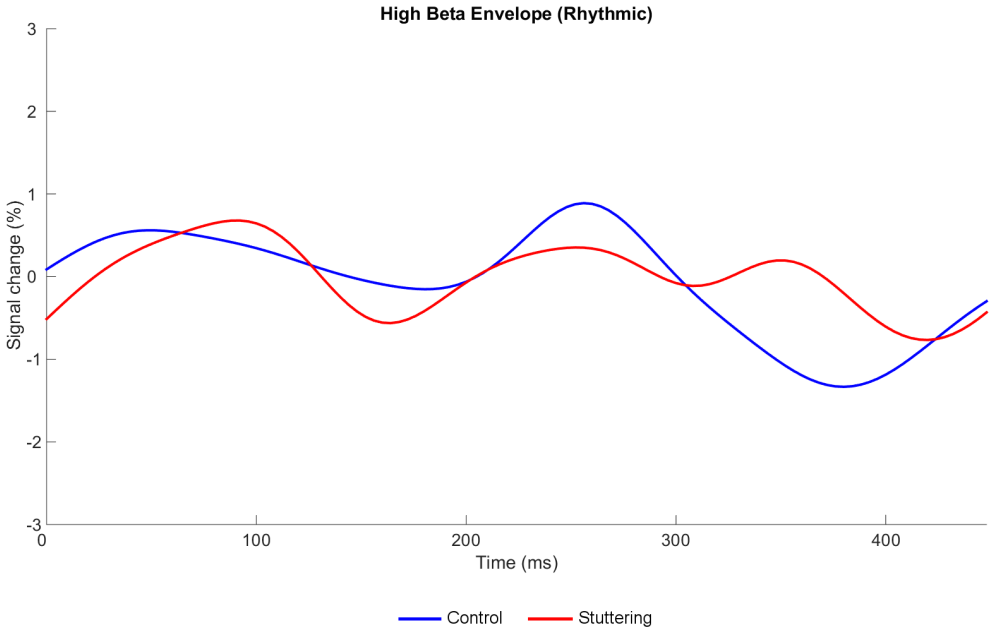

Figure 11.8: Time Frequency responses for the rhythmic condition. The plot depicts the percentage change of time frequency responses from the mean of the entire epoch for the control subjects (blue) against the stuttering subjects (red) from 0ms to 450ms relative to the onset of the tone. The grey areas depict time points at which there is a significant difference between groups (p=0.05 FDR corrected). N=10.

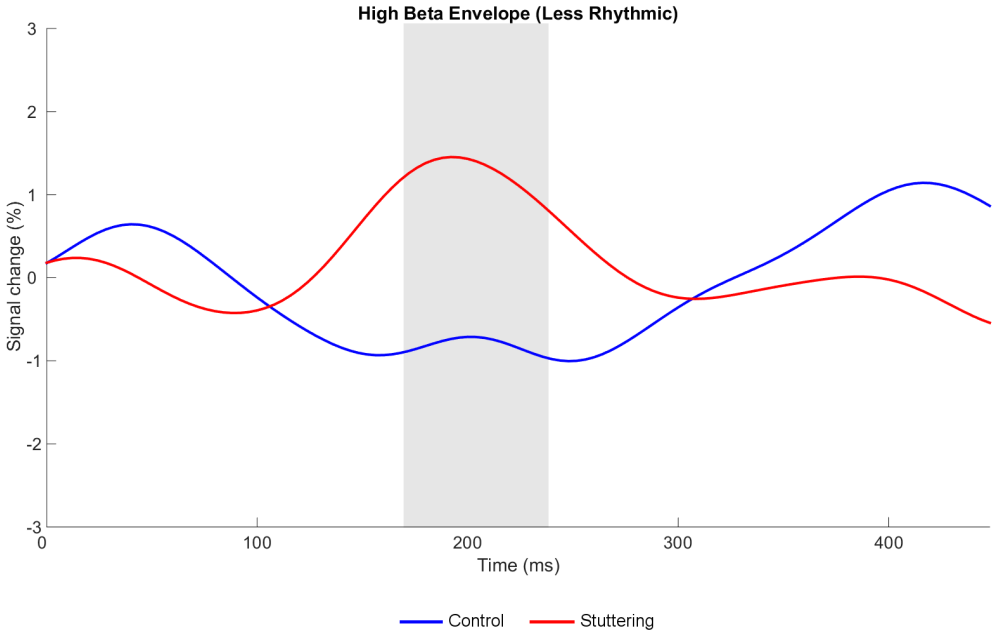

Figure 11.9: Time Frequency responses for the less rhythmic condition. The plot depicts the percentage change of time frequency responses from the mean of the entire epoch for the control subjects (blue) against the stuttering subjects (red) from 0ms to 450ms relative to the onset of the tone. The grey areas depict time points at which there is a significant difference between groups (p=0.05 FDR corrected). N=10.

11.4 Discussion

The present study aimed to investigate differences in neuromagnetic activity associated with rhythmic tracking between stuttering and non-stuttering children. Specifically, the envelope of the low beta band (12-15Hz) response was examined to rhythmic and less rhythmic trains of sounds while children passively watched a silent movie. Notably, this frequency range is slightly lower than the canonical 15-30Hz band commonly used to describe the beta band. Beta modulation in response to stimulation was maximally evident in both groups in this lower frequency range and this was also largely in agreement with a frequency range in which a previous study has found differences in connectivity of the 12-18Hz (the low beta band) between AWS and AWDS (Joos et al., 2014).

Consistent with the notion that beta band modulation reflects the internalization of temporal intervals (Cirelli et al., 2014; Fujioka et al., 2012), modulations were observed in low beta band activity in response to rhythmic sounds for stuttering and non-stuttering preschool-aged children. There was no evidence for tracking of rhythmic sounds in the high beta band (15-30Hz) in either CWS or CWDS. In addition, statistical comparisons of the low beta band envelope between the CWS and CWDS revealed that the pattern of beta band modulation in the less rhythmic condition resembled the beta band modulation in the rhythmic condition (i.e. there were no significant differences). A difference between CWS and CWDS in modulation of high beta band envelope in response to the less rhythmic tones was also recorded. There was however a noticeable difference between groups. Whereas typically developing children showed a peak in beta power close to the onset of the sound, stuttering chil-

dren showed a peak in beta power 225ms after the onset of the sound. The findings indicate that CWDS are largely consistent with the adults in the Fujioka et al. (2012) and Cirelli et al. (2014) studies in how they process rhythmic tones. Additionally, they indicate that CWS are less like healthy adults (as observed in Cirelli et al. 2014 and Fujioka et al. 2012) in their ability to utilise rhythmic cues: in contrast to CWDS, the beta band envelope of CWS did not peak near the time of the expected sound. This interpretation is further supported by the fact that in healthy adults, the presentation of the first stimulus in a sequence of auditory tones (as compared to subsequent presentations of the same tone) elicits an increase in beta power after (but not before) the onset of the stimulus, as compared to repeated presentations of the same sound (Haenschel et al., 2000). It would seem, therefore, that the pattern of beta band activity in the CWS is reactive rather than predictive. In agreement with the idea that the beta band reflects an internalization of the temporal interval, (Cirelli et al., 2014; Fujioka et al., 2012) these findings suggest stuttering is a disorder of internal timing (Alm, 2004; Etchell et al., 2014a; Chang and Zhu, 2013; Chang et al., 2015). Further, these results also may go some way to explaining why CWS are less accurate and more variable than CWDS when tapping to a beat at different tempos (Falk et al., 2014; Olander et al., 2010). In previous work, behavioural deficits in temporal processing were positively correlated with stuttering severity (Falk et al., 2015; Wieland et al., 2015). Such data was not collected in the present study because doing so places significant demands on their already limited attentional capacities. Nevertheless our findings suggest a likely neural correlate of a temporal processing deficit as per the contention of Fujioka et al. (2012) and Cirelli et al. (2014) who posit that the beta band is an index of the internal representation

of time. The difference in beta modulation in CWS may reflect an abnormal tracking ability that also impairs their speech production. These findings broadly agree with previous research showing a lack of synchronisation of beta band responses to single word production in AWS (Salmelin et al., 2000) and hypoactive beta band responses in CWS during rest as compared to hyperventilation (Özge et al., 2004). Although the studies above used very different experimental paradigms, it shows that CWS exhibit abnormalities in the time locking of the beta band envelope.

With respect to the less rhythmic condition, visual inspection revealed a relatively similar pattern of beta band activity found in the rhythmic condition. Although not perfectly consistent over the entire epoch, CWDS tended to exhibit peaks in beta band activity close to the onset of the stimulus and CWS exhibited a trough in low beta band activity (see Figure 11.3). This was partially supported by the results of the statistical analysis which showed a difference between the groups between 100-200ms (see Figure 11.5) as well as by an analysis of high beta band activity (in which CWS exhibited a peak between stimulus onsets). Interestingly, the CWS appeared to exhibit a more consistent beta band envelope than the CWDS. Because of the phase of the beta band envelope did not peak around the time of stimulus onset, I suggest the CWS react to, rather than predict, the stimuli. In contrast to the CWS, the CWDS exhibited a less consistent response perhaps because they had difficulty entraining to the less rhythmic stimuli. I was conscious of the fact that stimuli could occur at random between the 'average' interval of 450ms and potentially create differences in the beta band envelope between the rhythmic and less rhythmic conditions that are difficult to interpret. For instance, if a stimulus in the rhythmic condition occurred at 450ms after stimulus onset, and in the less

rhythmic condition, occurred at 300ms after stimulus onset, and resulted in a difference between groups, this difference might simply have resulted from the stimulus occurring at 300ms in that one condition. Despite the fact that I made no statistical comparison between the rhythmic and the less rhythmic condition, a pattern was still observed (in the less rhythmic condition) that bore some degree of visual similarity to the rhythmic condition. That is to say, for most (though not all) of the epoch, the modulation of the beta band in the less rhythmic condition seemed to exhibit peaks at about the same time as the rhythmic condition (see Figures 11.2 and 11.3). This result is not surprising as even the less rhythmic condition was still somewhat predictable, because the auditory stimuli could be expected within a certain time window (Fujioka et al., 2012; Cirelli et al., 2014). Therefore, as a result of the differences in the phase of the beta band envelope, it is tentatively suggested that CWS appear to be only reacting to the less rhythmic stimuli, while CWDS are attempting to predict or internalize it.

Group differences in beta envelope modulation identified here resembled a difference in phase of the beta band envelope and not a difference in beta band amplitude per se. The functional significance of this difference is not entirely clear, but may relate to the ability of CWS to utilise predictive cues to drive speech production. Indeed, a growing body of literature suggests that neural oscillations have a particularly important role in predicting when important information is going to arrive (Engel et al., 2001). It is known for example, that stimuli arriving at times of high excitability can be processed with maximum efficiency and be utilised to drive behaviour (Peelle and Davis, 2012). Additionally, the fact that neural oscillations must be realigned to match the expected occurrence of a sensory input necessitates

an adaptive process to adjust the timing of such oscillations. Moreover, the phase of ongoing oscillations that is normally reset by stimulus onsets, is also used to entrain brain signals to speech (Peelle and Davis, 2012). From our data, it seems either that CWS do not exhibit the same phase adjustment of the envelope of their neural oscillations that is seen in CWDS, or that the beta oscillations of CWS are not properly reset by stimulus onsets. It is possible that either of these factors may contribute to dysfluencies in speech that are characteristic of developmental stuttering. Accordingly, if the 'phase' difference is related to the cause of stuttering, then it may be beneficial to explore treatments options that could normalise the phase of such oscillations.

11.5 Limitations and Conclusion

A number of limitations in this experiment might have precluded the discovery of more widespread differences between groups. A frequent problem in studies investigating neurodevelopmental disorders like stuttering is that a large number of participants will spontaneously recover (Yairi and Ambrose, 1992, 1999). While this issue is often neglected, I feel that it is important to address because of how it shapes the interpretation of our data. The validity of comparing CWS and CWDS depends on whether or not the CWS can be classified as PWS. Although all children had a diagnosis of stuttering at the time of testing, it may be that some will recover because they lack the deficits in internal timing that lead to persistent developmental stuttering. More specifically, some of the stuttering children included in this study might not exhibit the behavioural variability in temporal processing -

or the corresponding neural activity - that may be predictive of a continuation of stuttering (Olander et al., 2010). In this view, the 'differences' in this study could be attributed to variations in normal developmental trajectories of entrainment to auditory stimuli as opposed to differences between CWS and CWDS. However, this assertion is challenged by Chang et al. (2008) finding that the brain structure of recovered CWS was more comparable to persistent CWS than to that of their fluent peers. Both persistent and recovered stutterers have less grey matter in the bilateral inferior frontal gyrus, the SMA and right temporal regions as compared to CWDS. That is to say, even if the vast majority of participants were to recover, their brains would more closely resemble CWS than control participants. Given the appropriate time and resources, future studies could incorporate a longitudinal examination of temporal processing in CWS and a retrospective analysis of the neural differences between recovered and persistent stutterers. This kind of study would both considerably further our understanding of how the neural correlates of temporal processing evolve with age in CWS, and determine the extent to which the phase of the beta band envelope in response to rhythmic and/or less rhythmic sounds is able to predict recovery or continuation of stuttering. While the CWS and CWDS were matched very closely in terms of both age and sex, they were not matched perfectly. While research is beginning to elucidate differences in neural activation between male and female CWS (e.g. Chang et al. (2015), the overall similarity of the groups suggests that the imperfect matching is unlikely to have affected the results, but is something that should be considered for future research.

In summary, I demonstrate the utility of investigating neural functioning in young children with and without developmental disorders. It is shown that CWS

exhibit differences in beta band modulation to rhythmic stimuli as compared to their typically developing peers. This evidence gives weight to the hypothesis that stuttering can be characterised as a disorder of internal timing and suggests that the neural mechanisms underlying temporal processing in stuttering warrants further investigation.

Chapter 12

General Discussion

12.1 Introduction

Speech production is very complex, requiring the coordination of over 100 different muscles. The purpose of speech, in a rather crude sense, is to convey information acoustically over time. This is achieved via the distribution of sequential auditory events over multiple timescales (syllables, words, sentences). When people speak, they routinely make predictions about what they will hear and when they will hear it. This is evidenced by a suppression of M100 amplitude to one's own speech (expected) relative to pitch shifted or alien feedback (unexpected) (Heinks-Maldonado et al., 2006). Individuals also make predictions about when they are likely to hear their speech. This is evident through observing the effects of delayed auditory feedback. The prediction of when particular events are likely to occur and making movement in time to a rhythmic constraint necessitates an internal representation of time. Temporal processing is therefore of fundamental importance to speech production. Self-paced movements such as those required to produce speech cause a change in the level of oscillatory activity in the canonical beta band (Marstaller et al., 2014), a part of the spectra of oscillatory brain activity thought to convey auditory to motor interactions (see Chapter 8). Deficits in the ability to perceive rhythms or produce movements in time with an external stimulus could adversely affect speech production. In the following sections, I briefly summarise each of the preceding chapters in this thesis before discussing the results of the experimental chapters in the context of fluent and dysfluent speech production.

In Chapter 2, I outlined developmental milestones in the acquisition of speech and the corresponding neural mechanisms that support this act. I highlight the

fact that speech is a very complex motor act, requiring coordination between many different regions of the brain and that previous models of speech production are greatly oversimplified.

Chapter 3 continued the discussion of normal speech production. It emphasised the importance of auditory and motor information for speech production in the context of recent models. predictive processes for fluent speech production. Specifically, I presented evidence that predictions about the content of upcoming words ('what') are influenced by temporal information. It then went on to discuss the importance of rhythm in normal speech production. Making predictions about the timing of upcoming stimuli is necessary for fluent speech. Since beta oscillations are modulated by both movement and the perception of tones (Fujioka et al., 2012) they may be modulated according to top down control of sensory regions by motor regions. If predictions of content and timing of speech are necessary for fluency, it stands to reason that abnormalities in the beta band would impact speech production.

In Chapter 4, I reviewed the last twenty years of neuroimaging research on developmental stuttering. This comprehensive summary of a large body of literature showed there are widespread differences in structure, function and connectivity in the brains of adults who stutter (AWS) and children who stutter (CWS) compared to their fluent peers. A brief summary of this research is presented below. Structurally, AWS tend to show reduced white matter compared to AWDS not only in auditory and motor regions of the brain but also differences in the fibres that connect them. (see for review Neef et al., 2015a and see alsoe.g. (Kronfeld-Duenias et al., 2014). Functionally, AWS tend to exhibit less left hempispheric activations and increased

right hemispheric activation (Budde et al., 2014; Belyk et al., 2015). AWS also exhibit atypical functional connectivity to subcortical regions like the basal ganglia (e.g. Lu et al., 2010b,a). EEG and MEG studies show that AWS differ from AWDS in the amount of motor preparation before speech onset and that they have less speech induced suppression of the response to hearing their own voice. A number of studies also indicate that AWS and CWS exhibit atypical brain responses during phonological and semantic processing. TMS studies show that AWS have reduced cortical excitability in speech and hand representations of the motor cortex, findings that are consistent with our proposal that stuttering is a more general deficit of motor timing. Among a number of other studies, there is evidence that fluency inducing conditions and speech therapy cause changes in the level of neural activity in AWS relative to AWDS regions including the cerebellum (Lu et al., 2012), basal ganglia (Ingham et al., 2013) and the inferior frontal gyrus (Kell et al., 2009). Finally, it was noted that despite widespread acknowledgement of the need to study CWS to better understand stuttering, there are very few neuroimaging studies of CWS.

Accordingly, Chapter 5 explored some potential reasons why there are so few studies on CWS. Similarly, a review of the perceptions surrounding the use of neuroimaging techniques and associated practical issues related to movement and attention was presented. While there are significant concerns regarding the use of neuroimaging methods like fMRI, MEG and EEG, these concerns can be mitigated. One of the solutions I proposed, and subsequently employed in the experimental chapters, is to use tasks that do not require overt responses (see Chapter 10 and 11 in which children watched a movie whist listening to trains of isochronous sounds).

Chapter 6 focused specifically on providing multimodal neuroimaging evidence that stuttering was a disorder of timing. It was argued that the internal timing network (ITN) consisting of the basal ganglia and supplementary motor area was impaired in stuttering and that deficits in this network could be compensated for by using the external timing network (ETN) consisting of the cerebellum and premotor area. There was a great deal of overlap in the networks involved in temporal processing and those thought to be associated with the either the cause of stuttering or compensation for stuttering. For example, the basal ganglia responds strongly to temporal regularities, is linked with self-paced (rather than externally-paced) movements, and exhibits structural abnormalities in CWS (Chang and Zhu, 2013). The problem that several behavioural studies indicated AWS do not differ from AWDS in the accuracy or variability of their tapping or motor movements, despite the contention that stuttering is a motor timing disorder, was also addressed. A proposal as to why AWS and AWDS might not differ behaviourally on timing tasks is that the brains of AWS are compensating for timing deficits via the right inferior frontal gyrus or the cerebellum. This clear hypothesis has not yet been investigated.

Chapter 7 proposed that deficits in neural mechanisms that support timing and rhythm in stuttering manifest in an abnormal appearance of oscillatory beta band dynamics. This contention was based on the idea that beta oscillations are linked to predictive processes, can be recorded in the basal ganglia and exhibit abnormalities in both AWS and CWS relative to their fluent peers. This dissertation specifically suggested that hyperactive (i.e. excessive) beta oscillations in AWS may reflect a compensatory process whereas reduced oscillations in CWS may reflect causal mechanisms.

The idea that stuttering is a disorder of temporal processing has gained significant traction in recent years. To this end, an increasing number of groups have been examining the possibility that stuttering is a disorder related to temporal processing deficit (e.g. Alm, 2004; Chang and Zhu, 2013; Chang et al., 2015; Etchell et al., 2014a; Falk et al., 2015; Toyomura et al., 2011, 2015; Wieland et al., 2015). The studies that have directly examined CWS support the idea that stuttering is a disorder of temporal processing. CWS have increased variability when tapping or clapping to a beat and CWS have functional and structural abnormalities in brain regions supporting temporal processing. The present series of experiments added to this growing body of literature by investigating whether oscillatory neural activity in the beta band is modulated differently in AWS and CWS relative to AWDS and CWDS during the perception and production of rhythms.

In the first study on AWDS, it was examined whether it was possibly to reliably detect beta band modulations during syncopation and synchronisation to a beat, and subsequently the direction of influence between the auditory and motor cortices. The pattern of beta modulation during the synchronisation and syncopation tasks was best explained by connections from the auditory to the motor cortex. This was somewhat expected given the fact that keeping in time often relies on external sensory feedback (Müller et al., 2000) and the saliency of the auditory stimuli. It perhaps suggests that in the presence of attention, a salient stimulus is able to drive activity in the motor cortex in a bottom up fashion (see Morillon and Schroeder 2015). Notably though, this result does not completely agree with the hypothesis of Arnal and Giraud (2012) which proposes that the motor cortex exerts control over the auditory cortex via the beta band. Interestingly however, the difference between

synchronisation and syncopation was best explained by connections in the forward and backward direction. Greater connectivity in the beta band for the syncopation task relative to the synchronisation task suggests that syncopation is more demanding than synchronisation. In line with this reasoning, previous work has observed that syncopated tapping elicited greater beta band activity than synchronisation tapping (Mayville et al. 2001; see also Manganotti et al. 1998) as well as the fact that internally timed movements require greater beta band power than those which are externally timed (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2015).

The second study compared the neural activity of AWS and AWDS during syncopation and synchronisation. Using beamformer-based virtual sensor analysis, the beta modulations in the auditory and motor cortices were examined. These areas are frequently observed to be active in finger tapping tasks (Chauvigné et al., 2014) and exhibit abnormal activations in AWS (Belyk et al., 2015; Budde et al., 2014). Within group comparisons revealed that AWS exhibited significantly greater beta band modulation in the syncopate condition as compared to the synchronise condition suggesting that syncopated tapping placed greater demands on internal timing systems than synchronised tapping. In contrast AWS showed a similar level of beta band activity for synchronise and syncopate tasks. Between group comparisons revealed that AWS had significantly more beta band activity than AWDS in the synchronise but not the syncopate conditions. In theory both syncopation and synchronisation involve the same pattern of movements. However, in practise, they are radically different. One reason why syncopation is more difficult than synchronisation and places more demand on systems governing timing is because of the way in

which movements are timed. With syncopation, a subject must predict not only the time of the sound, but also the time of the movement. As such, movement in syncopation may be organised in a more discrete fashion, on a trial by trial basis rather than in a continuous rhythmic sequence as in the synchronisation condition(Mayville et al., 2002). The observation of abnormal modulation during the synchronisation condition seems to suggest that AWS are performing the synchronisation task much in the same way as one would perform the syncopation task. Since these differences in neural activity occurred in the absence of differences in behavioural performance, they may reflect compensatory processes to a reduced level of beta activity elsewhere in the brain. Although speculative, it is possible that differences in beta oscillations between AWS and AWDS may occur as a direct result of deficits in beta band activity in the basal ganglia. Alternatively it might also suggest that AWS do not engage the structures required for internal timing as efficiently as AWDS. Given several reports of absences in behavioural differences in the production of rhythmic movements in AWS (e.g. Max and Yudman, 2003; Neef et al., 2011a), the results of the second experimental study highlight the need to consider the neural mechanisms of rhythm and timing in AWS.

While differences were recorded in beta band activity in AWS and AWDS, this does not guarantee that the same differences will be present in CWS. The observation of abnormal beta band dynamics in CWS would provide strong support for the idea that stuttering is a disorder of the internal timing of movements. Ideally, functional beta band activity during speech production in CWS would have been examined. However, conducting neuroimaging studies on children poses significant methodological challenges to researchers due to attention and movement restrictions

required for most tasks (see Chapter 5). For this reason, this dissertation opted to employ a rhythmic passive listening task known to elicit entrainment of the envelope of oscillatory beta band activity. Although this paradigm has been used in an MEG study of adults (Fujioka et al., 2012) and in an EEG experiment with children (Cirelli et al., 2014), it was not known if this was feasible to conduct the same experiment on children using MEG. Therefore, the third experiment aimed to test the feasibility of recording neuromagnetic beta band entrainment in children.

The third study demonstrated that CWDS exhibit beta band oscillations that exhibit an increase in modulation before the onset of the tone, similar to what has previously been found in adults (Fujioka et al., 2012) and children (Cirelli et al., 2014). These authors found that CWS were only able to 'track' the rhythm at 585 and 780ms tempo, but not at 390ms tempo. Notably, similar results were obtained when using the same frequencies. However at a lower frequency of 12-15Hz, it was found that envelope of the beta band tracks isochronous rhythms at all three tempi. Additionally, I observed a significant positive correlation between the envelope of beta band amplitude in the 585ms condition and age. This suggested that the ability to track rhythms at different tempi first begins to emerge at tempi corresponding to the spontaneous motor tempo (Drake et al., 2000). Furthermore, this dissertation demonstrates that CWDS exhibit a mismatch response to an unexpected change in tempo. This result is consistent with evidence that three day old infants are able to detect rhythm and changes in rhythm as evidenced by electrophysiological changes in evoked activity (Háden et al., 2015). Taken together, these studies demonstrate that the neural mechanisms that process rhythm are already established at an early age. The ability to perceive a rhythm may influence functions that develop later

in life. It is particularly interesting that the first semblance of speech - canonical babbling - is rhythmic, and emerges at the same time as other rhythmic behaviours such as (Ejiri, 1998), see also Kent et al. (1991)).

The fourth and final study focused on investigating differences in beta oscillations between CWS and CWDS in response to the perception of isochronous trains of sound. It was found that in contrast to CWDS, who showed a peak in beta band activity at the time of the sound, CWS exhibited a trough at the same time. This provided strong evidence that CWS show abnormalities in how their brains predict the onset of rhythmic sounds. More specifically, this is the first evidence that CWS differ from CWDS in how their brains perceive isochronous rhythms. The internal representation of time as indexed by the entrainment of the beta band envelope is abnormal in CWS. Because the pattern of beta oscillations in CWS seemed to be delayed relative to CWDS, it was suggested that CWS are exhibiting a reactive rather than a predictive pattern of beta band activity. This finding provides a possible neural correlate of behavioural work showing that CWS differ from CWDS in their ability to produce (Falk et al., 2015; Olander et al., 2010) or perceive (Wieland et al., 2015) a rhythm. My study also agrees with recent work showing that CWDS have abnormalities in the structure and resting state functional connectivity in that support the timing of self paced movements (Chang and Zhu, 2013). Finally, my study demonstrates that CWS exhibit abnormalities in the beta band at a very young age (see also Özge et al., 2004) that may be causally related to stuttering.

As mentioned at the beginning of this chapter, brain activity in the beta band is modulated by self paced movements (Bartolo et al., 2014; Bartolo and Merchant,

2015; Merchant et al., 2015) and temporally regular stimuli (Cirelli et al., 2014; Fujioka et al., 2012) and may convey both forms of information between areas of the brain. It was demonstrated that AWS exhibit abnormal beta band dynamics, to make the same simple rhythmic movements as AWDS. Additionally, it is presented here that CWS exhibit abnormal beta band dynamics at a young age. Together, this provides strong support for the idea that stuttering is a disorder of timing that has a neural marker in the structure of beta modulation. This is consistent with the ideas presented in Chapter 7 which links changes in oscillatory neural dynamics in the beta band to the aetiology of stuttering. However, although beta oscillations may be associated with stuttering, there remains a question of whether they are simply epiphenomenal or could actually be involved in moments of stuttering. The precise means by which abnormalities in the beta band could lead to stuttering has not yet been discussed. Therefore in the following sections, abnormalities in beta oscillations will be explored as a potential cause of stuttering. This includes a discussion of the relationship between the beta oscillations and the neurotransmitter dopamine (implicated in stuttering) and also neurocomputational models of stuttering that link these strands within a motor control framework. Although these ideas are speculative and were not investigated directly in this body of work, they are supported by experimental and theoretical evidence and provide an interesting insight into stuttering and a broader framework from within which the results of the current thesis might be viewed.

When a person speaks, a copy of the motor command (an efference copy) is sent to sensory regions of the brain and the timing and content of this prediction is compared with actual sensory feedback. This process is the basis of error detection

and correction in a number of motor control models. Recent work suggests that predictive feedforward commands and efference copies (Arnal and Giraud, 2012) are communicated via information contained in the oscillatory dynamics of the beta band. According to the GODIVA model of speech production, along with the motor command which initiates an utterance, an efference copy is sent to the basal ganglia to terminate the completion of the current syllable and to shift the articulators into a new position to produce the next syllable in a timely manner (Civier et al., 2013). Stuttering arises when a person attempts to transition to the next syllable at the wrong time. Here this dissertation suggests the inappropriate termination of the current syllable and/or initiation of the next syllable could be indexed by abnormalities in the phase and amplitude of the beta band envelope. It is further proposed that these abnormalities in the beta band arise because of elevated levels of dopamine in the striatum of AWS.

12.1.1 The beta band and dopamine

What is the relationship between dopamine and beta band oscillations? Beta band activity is inversely proportional to the level of dopamine in the brain: whereas a larger beta power is caused by low levels of dopamine, low levels of beta power is caused by a high level of dopamine (Jenkinson and Brown, 2011). It is well established that AWS have excess levels of dopamine in the striatum (Wu et al., 1997) which should result in differences in beta modulation in AWS. The contention that increased levels of dopamine should cause atypical beta band modulation is broadly in line with the result from chapter 9 which shows increased modulation of

beta band activity in AWS to AWDS during synchronisation tapping. How can this discrepancy be reconciled? Recall that this dissertation proposed elevated levels of beta band activity observed in AWS relative to AWDS at the cortex are likely to reflect compensation for reduced levels of beta band activity in the basal ganglia. If indeed this is the case, then, it would make sense that AWS have increased rather than decreased levels of beta band activity. CWS have not spent as much time stuttering as AWS. Because of this CWS show less extensive evidence of neural compensation (Chang and Zhu, 2013). This seems to apply to neural oscillations in the beta band as well. Özge et al. (2004) found reduced beta oscillations in CWS at rest. Thus the results of chapter 9 are not incompatible with the idea that increased levels of dopamine lead to reduced beta band activity.

This greater than normal level of dopamine may affect the brain in such a way that self-timed movements become substantially more difficult and have an adverse effect on the basal ganglia's ability to initiate the first syllable of a word (and manifests as a low level of beta band activity in the basal ganglia). Since larger beta power indexes longer durations between movements (Kononowicz and van Rijn, 2015), it follows that reduced beta power is a reflection of shorter durations. A shortened temporal duration between selection of the syllable and initiating motor movements could lead to premature articulatory movements. This idea is in line with the observation that administration of dopamine agonists (that increase the level of activity at dopamine receptors) speed up the internal clock, and that administration of dopamine antagonists (that decrease the level of dopamine) slow it down (Meck, 1996). This implies that, AWS who have excessive dopaminergic activity in the caudate (Wu et al., 1997) should have a faster internal clock and might therefore

expect sensory input earlier than it actually occurs. Such temporal mismatching between expectations of inputs and the timing of outputs could adversely affect when they should transition to the next syllable during speech production. This is indirectly supported by recent experimental evidence showing that CWS tend to tap far earlier in time than CWDS when synchronising finger taps with a beat or to music (Falk et al., 2015). Although no evidence of AWS tapping earlier in time than AWDS was found here, this may again be the result of neural compensation which would theoretically be greater in AWS than in CWS. A faster perception of time may be what contributes to stuttering.

Since the beta band is modulated by self-paced movements, areas of the brain that exhibit abnormally high or low levels of beta activity could be suggestive of deficits in internally timed or self-paced movements. For example, a low level of beta band power may indicate the basal ganglia is unable to send/receive motor commands to make sufficiently large articulatory movements necessary to produce the selected syllable. However, the low level of beta band activity may indicate that a person is able to make the small movements required to move the articulators into the initial position to produce the syllable. When this happens, blocking may result. This explains a number of important observations about stuttering. Firstly it accounts for why the articulators are in the initial starting position when a person stutters (Zimmermann, 1980) and fits with the claim that the magnitude of beta band power relates to the size of the movement to be executed (Arnal and Giraud, 2012). Secondly, it is consistent with the observation that stuttering tends to occur more on consonants, which require larger movements than the production of vowels. Other times, the first syllable of a word may have been correctly selected but the

brain might be unable to terminate the completion of the current syllable. If this is the case, then prolongations occur. This could occur because of abnormal beta band dynamics. More generally, the out of phase beta band oscillations it was observed in CWS relative to CWDS in Chapter 11 could directly affect the timing of information conveyed through via the beta band. If neural signals are not sent or received at the right time (i.e. when neural oscillations are at their peak Peelle and Davis 2012), the regions receiving these signals may have difficulty using the information. A consequence of this is that the basal ganglia will have difficulty sending/receiving the information contained in the beta band.

Imagine you had a faulty car horn that had a tendency not to work. You may attempt to press the horn multiple times in quick succession in the hope that at least one of the attempts will actually work. In the same way, an AWS may attempt to overcome blocks and prolongations by sending multiple motor commands to the basal ganglia. If motor commands are sent once the first syllable has been selected, but before the next syllable has been selected and motor signals are successful (as reflected by a series of desynchronisations in the beta band), then repetitions would occur. Repetitions of whole words/phrases may occur when the brain sends a sequence of motor commands to the basal prior to selection of the following syllable.

Dopamine antagonists might rectify the underlying neurological problem in stuttering (Maguire et al., 2004) by increasing beta band amplitude in the striatum (and other cortical areas). Since the beta amplitude is now larger, motor commands are more likely to be successful in moving the articulators to produce words. An indirect consequence of increased beta band amplitude is there is also no longer a

need to send multiple redundant motor commands to the basal ganglia. This is because auditory and motor information contained in the beta band is more likely to reach its target. Thus repetitions of whole words and phrases are also reduced. Dopamine antagonists would also slow the internal clock such that predicted sensory inputs are better aligned with actual sensory inputs. This would reduce instances of incorrectly timed transitions to the next syllable. Modulation of dopamine affects timing in the subsecond range (Rammsayer, 1999) and neural activity in the putamen (Coull et al. 2012; see also Wiener et al. 2011). If it is the case that stuttering is caused by abnormal beta band dynamics, then fluency inducing mechanisms should normalise beta band activity to some extent.

12.1.2 The beta band and fluency inducing mechanisms

How could fluency-inducing mechanisms influence beta band activity? There are several methods of inducing fluency in AWS and CWS. These include speaking in time with a metronome, another person (choral speech), delaying or masking auditory feedback and singing.

The basal ganglia is activated is response to rhythmic auditory stimuli (Grahn et al., 2007) and is responsible for self-timed movements (Merchant et al., 2015). The structure also exhibits structural and functional abnormalities in AWS (Lu et al., 2010b) and CWS (Chang and Zhu, 2013). In conjunction with the above evidence, the present series of studies, demonstrate that AWS have deficits in the timing of internally generated movements (see for review Etchell et al. 2014a) which may be reflected in atypical beta oscillations. The metronome produces a synchronisation ef-

fect whereby behavioural responses become synchronised with the metronome (Azrin et al., 1968). Beta band oscillations peak at the tempo of the metronome in cortical (Cirelli et al., 2014) and subcortical regions (Fujioka et al., 2012). This suggests that the basal ganglia exploits temporal regularities to synchronise movement (initiation and the termination of syllables) to the tempo of the metronome which could be directly correlated in the beta envelope peaking at the time of the sound.

Interestingly, Chapter 10 noted a positive correlation between the amplitude of the envelope of the beta band and age. This suggests that the ability to entrain to or predict the onset of stimuli develops with age. Chapter 11 found that CWS have difficulty entraining to some tempos and exhibit an out of phase beta band envelope to the onset of a sound as compared to CWDS. This indicates that CWS have trouble predicting the onset of sound at a very young age, even in the presence of what could be considered a fluency inducing mechanism. It further implies that atypical temporal prediction may be related to the cause of stuttering. This idea is supported by the fact that timing syllables to speech results in a 96% reduction in the number of stuttered syllable in preschool aged children (Trajkovski et al., 2011). Additionally, the beta amplitude could be directly affected by the interstimulus interval of the metronome. Slower metronomes lead to larger beta band responses (Kononowicz and van Rijn, 2015), which indicate the basal ganglia is able to shift to the next syllable. This may partially account for the observations that metronomes with a slower tempo tend to be more effective in inducing fluency than those with a faster rate (Hanna and Morris, 1977) whether or not a person speaks in time with the beat (Greenberg, 1970). The possibility that stuttering is causally related to abnormalities in the beta band is supported by a study from Özge et al. (2004) who found reduced

amplitude of beta oscillations in CWS as compared to CWDS during rest. Here is provided further evidence of abnormalities in the beta band of CWS. Although beta band amplitude was not directly examined in the study of CWS, the results of Chapter 11 highlight the fact that the pattern of beta envelope entrainment exhibits marked differences at a young age.

Another well-known fluency inducing mechanism is choral speech. Choral speech refers to when one person speaks in time with another person. Because choral speech already features an integration of speech and rhythm, it does not result in strong activation of the basal ganglia (Toyomura et al., 2011). Choral speech does however require AWS to correctly anticipate when they will hear speech and modify the timing of their motor movements so that their speech is in time with the acoustic information. Fluency may be improved because it brings the feedforward prediction of auditory feedback forward in time to match actual incoming auditory feedback. Using somewhat different terminology - synchronous speech - Cummins (2009) suggests acoustic information can be used to entrain motor movements of two speakers. Such entrainment may be manifest in beta band envelope peaking close to the onset of speech thereby increasing the likelihood of successfully transitioning from one syllable to the next.

Interestingly choral speech can work with auditory cues alone (Toyomura et al., 2011) or with visual cues alone (Kalinowski et al., 2000). This latter finding perhaps relates to the fact that visual cues (silent lip reading) precede and enhance entrainment to auditory cues (Peelle and Sommers, 2015). AWS may therefore be using the visual information (movement) to anticipate when they will hear their

own speech sounds. Some support for this comes from the fact that visual cues are sufficient to activate the auditory cortex (Calvert et al. 1997 during silent lip reading). More recently, Strelnikov et al. (2015) presented subjects with video clips in which a speaker did not emphasize any words (frequent stimuli) or emphasized a single word (deviant stimuli). Their results showed that viewing the infrequent condition elicited an MMN response that occurred after the start of the articulatory movements, but before the start of the auditory stimulus. Notably, this MMN response was not evident in the visual only condition where no auditory information was available. As such, the mechanisms by which choral speech and metronomes achieve their fluency effects may both be due to entrainment of articulatory movements to acoustic signals.

Delayed auditory feedback was originally an attempt to mimic choral speech. Instead of altering predictions about when sensory feedback is received (as in choral speech), delayed auditory feedback alters when actual sensory feedback is received. AWS may have a faster perception of time due to elevated levels of dopamine. There is some behavioural evidence that AWS have a faster perception of time (Barasch et al., 2000) than AWDS. Accordingly, AWS would expect sensory feedback before it actually occurs. How then does a further delay between expected and actual auditory feedback induce fluency? Increasing the delay between expected and auditory feedback could induce fluency in one of two ways. It could either alter feedforward predictions that are transmitted via the beta band to predict even later sensory feedback. Alternatively, it could create such a great mismatch that the brains of AWS discard the contents of the auditory feedback channel as meaningful, thereby eliminating any comparisons which in turn would eliminate the possibility of error detection. Interestingly Rastatter et al. (1998) found that AWS had heightened lev-

els of beta activity which was reduced by delayed auditory feedback. As proposed in Chapter 9, such hyperactivity is likely related to compensation for stuttering. delayed auditory feedback may therefore reduce the need for compensation that is manifested in excessive beta band oscillations rather than alleviating the underlying abnormality that is causing stuttering.

Masking auditory feedback may work in a similar way. Totally removing sensory feedback means that predictions propagating from the motor cortex to sensory areas cannot be invalidated by actual sensory feedback. Because sensory feedback is not invalidating the feedforward predictions from the motor cortex - efference copies sent via the beta band - error signals are not generated. The basal ganglia is thus able to initiate the transition to the next syllable because speech is not perceived as dysfluent.

There is evidence that invalidating visual cues with auditory information affects oscillatory activity in the beta (and gamma) band (Arnal et al., 2011). These authors examined the effect of auditory information on information that either validated or invalidated predictions gained from rhythm. As mentioned above AWS may have a tendency to make incorrect predictions about auditory information either during fluent speech or when they stutter. Presumably then, stuttered speech will exhibit differences in the beta band and gamma band similar to predictions made in the Arnal et al. (2011) study. Faulty predictions of sensory information would perhaps be corrected by synchronising auditory or visual information in the beta band with another speaker. This would enable AWS to more accurately predict their own auditory feedback. Fluency inducing mechanisms may have similar effects on the

brain such that feedforward predictions become more accurate, perhaps manifested in beta band oscillations as per the Arnal et al. (2011) study.

Singing does not require (as much) shifting between syllables. It also utilises many different neural structures but, unlike speech, tends not to engage the basal ganglia (Özdemir et al., 2006). However, singing does result in greater beta band activity than speech (Gunji et al., 2007), perhaps due to the emphasis singing places on rhythm and timing (Alm, 2004).

The above sections proposed a more direct link between dopamine, beta band activity and stuttering. Furthermore, a link between fluency inducing mechanisms to the beta band has been examined. Many of the ideas presented here are speculative and remain to be verified by future research. To our knowledge, no study has investigated the effects of fluency inducing mechanisms on beta band activity during speech in AWS. As such, the ideas presented here offer several opportunities for future work to investigate oscillatory activity in AWS and CWS, an area that has largely been neglected.

12.2 Limitations and Conclusion

Although they yielded promising results, the present series of studies had some limitations. First and foremost, while all AWS and CWS had been diagnosed as having stuttering, the severity of their stuttering as assessed on the day of their participation in the experiments, was low. This may be due to the fact that only audio data in the speech sample was collected. Indeed recent work suggests that audiovisual recordings lead to an 18% higher estimate in the percentage of syllables stuttered as

compared to audio recordings alone (O'Brian et al., 2015). Further, while data was gathered regarding whether or not a subject had undergone therapy for stuttering (all except for one CWS had undergone therapy), no information was gathered about the duration of treatment (particularly for the children). This was less than ideal. However, since there was no attempt to calculate correlations between stuttering severity and beta band modulation, the lack of stuttering severity is moot. The observation of differences in beta band modulation even at relatively low levels of stuttering severity suggests that such differences are robust. In future (and with a larger sample), it would be beneficial to take more accurate measures of stuttering severity and examine how this might correlate with beta band modulation as well as gathering a more detailed record of therapy.

A second limitation concerns the investigation of a limited subset of regions of the brain. While there are a wide variety of cortical and subcortical regions involved in both sensorimotor synchronisation (Chauvigné et al., 2014) and listening to isochronous tones (Fujioka et al., 2012) the current series of studies (Chapters 8-11) only examined beta band oscillations in auditory and motor regions. Examining how the gamma frequency band (and others) differ between PWS, PWDS, experimental conditions and the beta band would be particularly enlightening and is something to consider for future work. Other brain areas such as the basal ganglia are crucially involved in stuttering (Alm, 2004). However, activity subcortical regions were not examined. This is partly because of debate over whether MEG can detect subcortical sources like the basal ganglia (see for review Attal et al. 2012, thought it is not impossible (e.g. Fujioka et al. 2010; Ng et al. 2013). Theoretically, if there were differences between AWS and AWDS in the level of beta modulation in the basal

ganglia then it is possible that they were undetectable due to the limited spatial resolution of MEG. This is compounded because subcortical regions like the basal ganglia are generally far away from the MEG sensors and are hard to measure. Furthermore, recording oscillatory activity directly from the putamen is impractical under most circumstances. For this reason, it is difficult to verify whether AWS or CWS exhibit abnormalities of beta band power/envelope-phase in the putamen.

The results reported here offer several directions for future research. There remain a number of outstanding questions. Because the time-frequency data reported here are normalised to the entire epoch (dictated by the continuous nature of the task and the desire to make our results consistent with (Cirelli et al., 2014; Fujioka et al., 2012). Therefore comments about the absolute levels of beta amplitude per se cannot be made. However, given the differences in beta modulation between AWS and AWDS, future work may wish to examine absolute differences in beta band power. This may include using MEG to examine how beta band power is modulated during speech production and in the presence and absence of fluency inducing mechanisms like delayed auditory feedback, metronomes and choral speech. In a similar vein it could be interesting to assess whether there are difference in beta band activity between AWS, CWS and their fluent peers during perturbations of auditory feedback. If stuttering is related to abnormalities in beta band oscillatory dynamics, it would be expected that there are likely to be differences in the amplitude and/or phase dynamics without fluency inducing mechanisms. Along a similar line of reasoning, how does beta band activity relate to sensory feedback during speech? It would be interesting to use DCM in conjunction with MEG to examine how perturbations of time and pitch affect the directionality of oscillatory responses between sensory and

motor areas.

If the out of phase beta band response observed was causally related to stuttering, then perhaps disrupting the phase of the envelope could transiently induce stuttering. This may work by disrupting the predictive mechanisms associated with top down control. It might be possible to induce stuttering by using repetitive TMS to introduce noise into areas that integrate auditory and motor information (e.g. area SpT see Hickok et al. 2011). Another possibility is to examine the effects of applying repetitive TMS on the behavioural performance of AWS and AWDS on tasks requiring the estimation or production of different temporal intervals. Theoretically these effects could then be reversed to enhance, or even be used in place of, current treatments (see for example Krawinkel et al. 2015).

Currently there is little functional neuroimaging data available for CWS with respect to speech production (see Sowman et al. 2014 for an exception). The experiments reported here could be replicated in AWS or AWDS with fMRI to determine whether there are differences in BOLD activity during synchronised/syncopated finger tapping. Further, in light of experimental paradigms that can reliably detect haemodynamic responses in a short period of time (see Loucks et al., 2011), it would be interesting to see how CWS respond to speech using fMRI or MEG.

Another intriguing possibility is to examine time perception in AWS and CWS. If it is true that they have excess levels of dopamine and this leads to a faster internal clock, then AWS should have a faster perception of time. This could be reflected behaviourally through tasks that examine time estimation (e.g. Rao et al., 2001) and perhaps also in the accumulation of neural activity over time as measured

by fMRI, MEG or EEG.

hspace6ex In the above experiments, this dissertation provides novel evidence that stuttering is associated with abnormalities in oscillatory beta band dynamics. This is evident through AWS exhibiting greater than normal levels of beta band activity during synchronised tapping as relative to AWDS. Moreover, the level of beta oscillations required for simple rhythmic movements is similar to those required for more demanding syncopated movements. It was shown that CWDS exhibit a beta band response similar to that of adults during the perception of multiple isochronous intervals. Additionally, evidence of CWS exhibiting an out of phase modulation of the beta band envelope compared to CWDS when listening to isochronous tones at 450ms SOAs is presented. These findings provide a novel insight into the perception and production of rhythm in stuttering.

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Appendices

Appendix B.

Table of Neuroimaging Studies on AWS

Study	Method	Sample	Task	Main Finding height
Fox et al. (1996)	PET	10M AWDS (21-55) 10M AWS (21-46)	Chorus vs. Solo Reading	AWS had overactivation in motor areas that was reduced by choral reading
Ingham et al. (1996)	PET	19M AWDS (21-55) 10M AWS (22-46)	Resting State	AWS and AWDS do not differ in cerebral blood flow at rest
Braun et al. (1997)	PET	12M 8F AWDS (23-50) 10M 8F AWS (23-51)	Fluency vs. Dysfluency	Activation of LH and RH associated with stuttered and fluent speech respectively
Wu et al. (1997)	PET	6M AWDS (-) 3M AWS (-)	Resting State	AWS had higher uptake of FDOPA than AWDS throughout cortex
Morgan et al. (1997)	EEG	8M AWDS (17-36) 8M AWS 17-36)	Oddball Task	5 of 8AWS had higher P300 in LH and AWDS had higher P300 in RH
Rastatter et al. (1998)	EEG	6M AWDS (16-44) 6M AWS (16-45)	Delayed vs. Non altered auditory feedback	AWS show a decrease in beta activity under delayed auditory feedback
Salmelin et al. (1998)	MEG	8M 2F AWDS (25-52) 7M 2F AWS (22-53)	Neural responses to tones during overt, cover and choral reading	AWS had larger M100 responses to tone during choral reading
DeNil et al. (2000)	PET	10M AWDS (20-25) 10M AWS (24-44)	Silent vs. Oral Word Reading	AWS showed greater RH activation and AWDS showed greater LH activation when comparing oral vs silent reading.
Fox et al. (2000)	PET	10M AWDS (32) 10M AWS (32)	Solo, Choral Reading and Rest	Brain correlates of stuttering are non dominant left hemisphere
Ingham et al. (2000)	PET	4M AWDS (28-50) 4M AWS (30-46)	Solo vs. Choral Paragraph Reading vs. Rest	Imagined stuttering elicits brain activation associated with overt stuttering
Khedr et al. (2000)	EEG	20M 5 F AWDS (6-25) 31M 6F AWS (6-25)	Oddball Task	AWS do not have a deficit in attention or cognitive processing as indexed by P300
Salmelin et al. (2000)	MEG	8M 2F AWDS (25-52) 7M 2F AWS (22-53)	Word Reading and Finger Movements	Sequence of brain activation was normal in AWDS but reversed in AWS
DeNil et al. (2001)	PET	10M AWDS (20-45) 13M AWS (20-45)	Silent and Oral Reading, Verb generation vs. Passive Viewing	Fluency Treatment increased cerebellar activation
Foundas et al. (2001)	sMRI	13M 3F AWDS (31.72) 13M 3F AWS (31.72)	N.A	AWS had a larger planum temporale than AWDS
Weber-Fox (2001)	EEG	7M 2F AWDS (17-34) 7M 2FAWS (17-34)	Covert Sentence Reading	AWS had reduced amplitude to all conditions between 200-450ms relative to AWDS
Sommer et al. (2002)	DTI	11M 4F AWDS (23-43) 10M 5F AWS (18-44)	N.A	AWS have reduced white matter integrity in the left tongue/laryngeal representation of the motor cortex relative to AWDS
Foundas et al. (2003)	sMRI	13M 3F AWDS (29.63) 13M 3F AWS (33.81)	Task	AWS did not have a larger right than left prefrontal lobe volume or larger left than right occipital lobe volume normally seen in AWDS

Study	Method	Sample	Task	Main Finding height
DeNil et al. (2008)	fMRI	15 AWDS (21-48) 15 AWS	Listen, Vocalise, simulate stuttering and prolong a word	AWS showed significantly more activation in bilateral cortical regions during normal speech. AWS showed significantly more activation in the right inferior frontal gyrus than AWDS when simulating stuttering.
Giraud et al. (2008)	fMRI	16 AWS (18-48)	Reading sentences vs. silent viewing of meaningless letter like signs	Activity in basal ganlgia (caudate) positively correlated with stuttering severity before speech therapy but not after (except for a small cluster)
Hampton and Weber-Fox (2008)	EEG	8M 3F AWDS (19-60) 8M 3F AWS (18-62)	Oddball paradigm	No statistical difference between amplitude or latency of P300. Individual differences showed AWS P300 to deviant tones tended (though not significantly) to be reduced in compared AWDS.
Weber-Fox et al. (2008)	EEG	8M 2F AWDS (9-13) 8M 2F AWS (9-13)	Listen to canonical sentences containing a verb agreement/violation and a semantically unexpected verb	AWDS exhibited an N400 for reduced semantic expectations and a P600 for verb agreement violations. AWS exhibited an N400 and a P600 for both conditions
Chang et al. (2009)	fMRI	9M 11F AWDS (36.35) 11M 9F AWS (36.35)	Perceive plan and produce speech	AWS exhibited reduced activation of motor regions during perception and greater activation in motor and auditory regions during production. Differences were similar for speech and non speech stimuli.
Kell et al. (2009)	fMRI and VBM	13M pAWS (18-39) 13M rAWS (16-65) 13M AWDS (23-44)	Overt sentence reading vs. covert sentence reading (baseline) before and after therapy	Persistent stuttering associated with mobilization of regions contralateral to (predominantly left sided) structural abnormalities. Optimal repair associated with engagement of left BA47/12
Lu et al. (2009)	fMRI (SEM)	9M 1F AWS (20-29) 5M 4F AWDS (22-29)	Covert picture naming vs passive viewing (baseline)	AWS exhibit large scale dysfunctional neural interactions across widely distributed brain regions, particularly those involved in auditory and motor processing.
Sakai et al. (2009)	fMRI	3M 5F AWS (20-53) 3M 7F AWDS (24.1)	Sentence reading during delayed and normal auditory feedback vs. Passive viewing of fixation cross	AWS show greater activation of the right inferior frontal gyrus during normal speech. AWS had less activation of the right SMA and STG in both conditions.
Sommer et al. (2009)	TMS (MEP, iSP)	15 AWS (28.7) 15 AWDS (26.7)	Paired pulse stimulation Recorded MEP's from the abductor digiti minimi	No difference between groups for interhemispheric inhibition or the ipsilateral silent period. AWS have normal inter-hemispheric inhibition.
Beal et al. (2010)	MEG	12M AWS (21-45) 12M AWDS (24-49)	Listen to tones, listen to vowels /i/, listen to words (pre-recorded), produce vowels /i/, produce words	AWS exhibit a similar amplitude of speech induced suppression to AWDS. AWS had earlier right than left hemispehre M100 and AWDS did not.
Cykowski et al. (2010)	MRI (DTI)	13 AWS (31) 14 AWDS (30.4)	N/A	AWS showed a reduction in fractional anisotropy in left perisylvian regions. These were driven by an increase in radial diffusivity (perpendicular to fibre tracts)

Study	Method	Sample	Task	Main Finding height
Lu et al. (2010b)	fMRI (SEM and VBM)	10M 2F AWS (19-31) 9M 1F AWS 8M 4F AWDS VBM (22-29) 5M 4F AWDS for SEM	Picture naming task vs. passive viewing task (baseline); baseline task first then naming task	AWS had weaker connections throughout BGTC network. AWS showed corresponding reductions in GMV in the left putamen, MFG and ASTG. And less white matter in the left posterior superior temporal gyrus
Lu et al. (2010a)	fMRI (SEM)	10M 2F AWS (20-29) 7M 5F AWDS (22-29)	Picture naming a one or three syllable word or repeating the one syllable word 3x	AWS exhibited atypical planning in the bilateral inferior frontal gyrus and right putamen. AWS exhibited atypical production in the right cerebellum, insula and left premotor area.
Liotti et al. (2010)	EEG	8M AWS (27-56) 8M AWDS (25-55)	Produce vowels 'ah' and Listen to vowels 'ah' (recording of produced sounds)	No difference in N1 speech suppression between AWS and AWDS for speech induced suppression. AWS exhibited early N1 in listen condition relative to AWDS
Maxfield et al. (2010)	EEG	12M 2F AWS (19-52) 7M 7F AWDS (19-45)	Word reading: + fixation (550ms), line drawing (450ms), blank screen (200ms), auditory probe word, cue (!!!)	AWS showed a enhanced N400 amplitude in response to semantically related as compared to unrelated probes whereas AWDS showed a reduction in N400 amplitude for the same trials.
Arnstein et al. (2011)	EEG	10M AWS (35.7) 10M 3F AWDS (25.6)	Rhyming judgement task Flanker task	AWS exhibited a larger error related negativity than AWDS regardless of the accuracy of their responses
Chang et al. (2011)	fMRI and DTI	13M 10F AWS (35) with fMRI 12M 11F AWDS (33) with fMRI 9M 6F AWS (36) with DTI 7M 7F AWDS (33) with DTI	See Chang et al., (2009)	AWS had atypical structural and functional connectivity from the left inferior frontal gyrus to premotor regions but only atypical functional connectivity in the BGTC pathway
Choo et al. (2011)	MRI (VBM)	11M AWS (20-35) 12M AWDS (20-35)	NA	AWS had a larger rostrum and anterior midbody of the corpus callosum than AWDS. AWS had an overall larger callosa than AWDS.
Kikuchi et al. (2011)	MEG and MRI (VBM)	17M AWS (21-41), 18M AWDS (22-43)(Exp 1) 16M AWS (21-41), 16M AWDS (22-43) (Exp 2) 15M AWS (21-41), 15M AWDS (22-43) (Exp 3)	Exp1. (Auditory Sensory Gating) 3ms monaural clicks presented with 500ms ISI and an ITI between 8-12 seconds; Exp2. (Tonotopic organization) 128+ 300ms, tones at 250,1000, 4000Hz presented with ISI between 2.5-3.5 seconds Exp3. (VBM)	AWS lack the P50 supression of a second tone normally observed in AWDS. Right hemisphere earlier than left hemispehre in AWS but not in AWDS. AWS showed a significant increase in GMV in the right STG.
Loucks et al. (2011)	fMRI	10M 1F AWS (25.9) 9M 1F AWDS (25.2)	Oral Picture Naming, Silent auditory phoneme monitoring vs. silent rest (baseline)	During picture naming, AWS showed higher activity in the right inferior frontal gyrus, temporal lobe and sensorimotor cortices relative to AWDS.
Neef et al. (2011a)	TMS (MEP)	9M 3F AWS (29.9) 9M 3F AWDS (29.5)	Experiment 1: Active Motor Threshold Paired Pulse Stimulation Experiment 2: MEP's during active motor threhsold	AWS exhibit a reduced and delayed short intracortical inhibition the right hemisphere and reduced intracortical facilitation in both hemispheres relative to AWDS. AWS also show a steeper MEP recruitment curve than AWDS
Neef et al. (2011b)	Repetitive (inhibitory) TMS	13M 1F AWS (30.3) 14M 1F AWDS (28.1)	repetitive TMS applied over the left or right dorsolateral premotor cortex before paced finger tapping (in different blocks).	In AWS inhibition of the right dorsal premotor cortex impaired synchronisation accuracy of the left hand whereas in AWDS inhibition of the left dorsal premotor cortex impaired synchronisation of the left hand.
Sassi et al. (2011)	EEG	6 AWS (24.5) 6 AWDS (21.6)	Oddball paradigm: 1000Hz standard tone (80%), 1500Hz deviant tone (20%). Participants to raise finger upon hearing deviant.	There was no significant difference in amplitude or latency of the P300 before or after treatment.
Toyomura et al. (2011)	fMRI	11M 1F AWS (18-55) 11M 1F AWDS (22-44)	Sentence reading (solo, metronome or chorus)) vs. Rest (baseline).	AWS exhibit reduced activity in the caudate during solo reading. This was increased to the levels of AWS in the metronome condition but not the chorus condition. Basal ganglia was negatively correlated with stuttering severity.
Howell et al. (2012)	fMRI (SEM)	7M 2F AWS (20-29) 5M 4F AWDS (22-29)	Picture naming (in mandarin). Pictures could be named by characters with the following tones: high-flat, rising, falling-rising, and falling vs. passive viewing unnamable pictures (baseline)	AWS lack functional connections between the insula and left laryngeal motor cortex. AWS also have connections between the putamen and the left laryngeal motor cortex which are not seen in AWDS.

Study	Method	Sample	Task	Main Finding height
Ingham et al. (2012)	PET	18 AWS (20-67) 12 AWDS (20-65)	Eyes closed rest, Eyes Open rest, oral reading aloud (reading text aloud), monologues (continuous self formulated speech)	AWS and AWDS show few differences in functional activation. Differences in activation during speech produciton were also seen during resting state. Stuttering frequency associated with activity in the cortico-striato-thalamic network
Jiang et al. (2012)	fMRI	20 AWS (26.8)	Sentence completion task with same grammatical structure vs. resting	Whereas the left inferior frontal gyrus and the bilateral precuneus showed higher brain activity to most typical than least typical symptoms, the left putamen and the right cerebellum show the most activation for the least typical symptoms.
Lu et al. (2012)	fMRI	15 AWS (24) 13 AWDS (24)	Resting state connectivity compared before and after speech therapy (eyes closed)	Resting state functional connectivity in the cerebellum was reduced following therapy but functional connectivity in the left inferior frontal gyrus was unchanged.
Maxfield et al. (2012)	EEG	11M 3F AWS (32.4) 2M 12F AWDS (23.6)	Picture naming	AWS exhibited reduced semantic priming and reversed phonological priming (enhancement of N400 amplitude) for phonologically related as opposed to phonologically unrelated probes.
Alm et al. (2013)	TMS (MT)	14M 1F AWS (20-52) 14M 1F AWDS (20-52)	TMS induced MT of the ADM muscle; compared motor threshold between individuals	AWS had a higher motor threshold (MT) in the left hemisphere as compared to their own right hemisphere MT. AWS also had a higher MT in the left hemisphere compared to the AWDS left hemisphere MT.
Busan et al. (2013)	TMS (MEP)	11M 6F AWS (19-46) 17M 6F AWDS (20-43)	Resting and Active motor threshold silent period of the FDI muscle	AWS showing reduced resting MEP amplitude compared to AWDS in the left hemisphere when averaged across all stimulus intensities.
Ingham et al. (2013)	PET	17M 5F AWS (20-64) 8 AWDS (20-64)	PET scan before and after treatment During the PET scan, SSX performed oral reading, monologue and eyes closed rest (baseline).	Decreased regional cortical bloodflow in the left putamen was predictive of successfully completing the treatment program.
Wymbs et al. (2013)	fMRI	4M AWS (19-25)	Overt and covert of (stutter prone and non stutter prone words	AWS exhibited consistnet activations when scanned on two different occasions. AWS did not show strong overlap between different individuals during overt and covert stuttering
Cai et al. (2014b)	MRI (DTI, network based statistics)	15M 5F AWS (18-47) 14M 4F AWDS (19-43)	NA	AWS exhibited reduced fractional anisotropy in the left mid motor cortex and reduced connectivity with other corical brain regions as compared to AWDS. This reduction also positively correlated with stuttering severity.
Joos et al. (2014)	EEG (Oscillations)	11 AWS (27.8) 11 AWDS (28)	Resting State EEG (eyes closed)	No significant differences between AWS and AWDS resting state functional activity. However, AWS exhibited decreased functional connectivity in beta band between left BA4/45 and contralateral premotor and primary motor areas.
Kronfeld-Duenias et al. (2014)	MRI (DTI)	12M 3F AWS (31.7) 16M 3F AWDS (33.26)	NA	AWS exhibit increased mean diffusivity of the frontal alsant tract. The diffusivity values measured in the FAT negatively correlate with speech fluency. mean diffusivity predicts mean speech rate only in AWS.
Tahaei et al. (2014)	EEG	21M 4F AWS (16-35) 21M 4F AWDS (16-25)	Auditory brainstem responses to speech sounds (synthesized syllable /da/ with a duration of 40ms)	AWS have significantly increased latencies for the onset and offset waves of V, A and O waves to speech ABR. AWS showed deficient timing in early neural response to speech sounds consistent with temporal processing deficits.
Cieslak et al. (2015)	MRI (DSI)	8 AWS (20-39) 8 AWDS (20-31)	NA	AWS were missing missing large portions of the bilateral arcuate fasciculus. AWS also had a connection from the cortico-spinal tract to the temporal cortex that was not seen in AWDS.
Civier et al. (2015)	MRI (DTI)	11M 3F AWS (19-52) 11M 3F AWDS (19-47)	NA	AWS show reduced fractional anisotropy in the anterior corpus callosum. This reduction is positively correlated with a reduction in speech fluency. Likely represents weaker inhibition of the right frontal cortex

Study	Method	Sample	Task	Main Finding height
Daliri and Max (2015)	EEG (evoked)	11M 1F AWS (18-46) 11M 1F AWDS (19-45)	Overt and covert reading and viewing ++++++ Presented a tone 400ms after word onset on 1/3 of the trials in each condition	AWS did not show a reduction in N1 amplitude to sounds prior to speech whereas AWDS did.
Maxfield et al. (2015)	EEG (Evoked)	13M 6F AWS (26) 14M 5F AWDS (24)	Fixation (500ms), pattern mask "#####" (200ms), prime word (identity or control), 70ms, backward mask (8 consonants, 50ms), picture (remained until response)	Priming improved reaction times in both AWS and AWDS. P1 amplitude correlated with expressive vocabulary in AWS but expressive vocabulary in AWDS. Identity priming reduced P280 amplitude in AWS.
Mock et al. (2015)	EEG	12M AWS (23-54) 12 AWDS (23-55)	Cued or uncued picture naming with an early or late probe	Negative slow wave associated with efference copy was smaller in AWS relative to AWDS
Neef et al. (2015b)	TMS (MEP)	9M 4F AWS (21-55) 9M 4F AWDS (23-44)	Measured MEPs during speech	AWS lacked an increase in cortical excitability in the left hemisphere that was seen in AWDS. Negative correlation between facilitation and stuttering severity indicates pathophysiological role in the disorder
Toyomura et al. (2015)	fMRI	10 AWS (20-31) 10 AWDS (22-23)	Self vs. externally paced sentence reading, to the sound of the metronome, and rest (baseline). Tested before speech therapy (1 scanning session) and after speech therapy (another scanning session).	Before treatment AWS showed significantly less activation than AWDS for both the self and external condition in the putamen, caudate and globus pallidus. After treatment, there was no difference in the activaiton between AWS and AWDS.
Vanhoutte et al. (2015)	EEG	19M 6F AWS (18-57) 24M 11F AWDS (18-58)	Picture naming task: Warning stimulus (S1 Picture presented for 1000ms), then a 1000ms blank interval, and a imperative stimulus (S2, black line presented for 2000ms) and then a black screen (presented for a further 2000ms). name picture at (S2)	AWS show an increased CNV slope as compared to AWDS. Slope of CNV positively correlates with stuttering severity and frequency. Cortical basal ganglia loop is overactive during speech motor preparation in AWS.

Appendix B.

Table of Neuroimaging Studies on CWS

Study	Method	Sample	Task	Main Finding height
Özge et al. (2004)	EEG	21 CWDS (3-12) 26 CWS (3-12)	Hyperventilation vs. Resting	Amplitude of delta and theta wave is increased in CWS relative to CWDS. Amplitude of and beta band alpha is decreased relative to CWDS.
Chang et al. (2008)	MRI (DTI)	8M pCWS (9-12) 7M rCWS (9-12) 7M CWDS (9-12)	N/A	Risk of lifetime and persistent stuttering associated reduced GMV and WMV in left hemisphere respectively. Right hemisphere overactivations in AWS likely result of compensation as absent in CWS
Weber-Fox et al. (2008)	EEG	8M 2F CWS (9-13) 8M 2F CWDS (9-14)	Judge whether or not a target word rhymes with a orthographicaly similar/dissimilar prime word	Latency of N400 earlier in left hemisphere than right hemisphere for CWDS, but similar latency between the left and right hemisphere for CWS
Özcan et al. (2009)	EEG	16M 4F CWS 7-18) 16M 4F CWDS 7-18)	Listen to 2 successive 'click' sounds of 100ms duration	CWS and CWDS are no significantly different in terms of the amplitude or latency of the P50 suppression.
Kaganovich et al. (2010)	EEG	13M 5F CWS (4-6) 12M 6F CWDS (4-6)	Oddball paradigm 1000Hz (standard) and 2000Hz tones (deviant) presented monaurally and binaurally	CWDS but not CWS exhibited significant P3 to deviant tones
Beal et al. (2011)	MEG	11M CWDS (6-12) 11M CWS (6-12)	Produce vowel sound 'a'	Both CWDS and CWS show suppression of auditory M50; CWS had a delayed M50 latency relative to CWDS
Sato et al. (2011)	NIRS	10M AWS (18-44) 5M 2F CWS (6-12) 5M 1F preschool CWS (3-5)	Listen to phonemic contrast (/itta/ vs. /itte/ or prosodic contrast /itta/ vs. /itta?/)	AWDS and CWDS showed LH advantage for phonemic vs. prosodic contrast; AWS and CWS did not show laterality difference between conditions; Lateralization for speech processing abnormal in preschool CWS
Choo et al. (2012)	MRI (VBM)	8M pCWS (9-12) 6M rCWS (9-12) 7M CWDS (9-12)	N/A	No difference in corpus collosum or WMV between pCWS, rCWS and CWDS; right hemisphere differences in adults likely result of compensation
Mock et al. (2012)	MRI (DTI)	14M CWS (8-13) 14M CWDS (8-13)	N/A	Stuttering is associated with atypical brain torque in prefrontal areas; CWS had more WMV in left and right hemispheres; positive correlation between left prefrontal WMV and dysfluency rate
Beal et al. (2013)	MRI (VBM)	11M CWS (6-12) 11M CWDS (6-12)	N/A	CWS had reduced GMV in left inferior frontal gyrus and putamen and increased GMV in right inferior frontal gyrus and superior temporal gyrus as compared to CWDS
Chang and Zhu (2013)	MRI (DTI)	27 CWS (3-9) 29 CWDS (3-9)	Resting State	Basal ganglia thalamo-cortical network develops abnormally in CWS. Abnormal function in CWS as compared to CWDS.
Foundas et al. (2013)	MRI	14M CWS (8-13) 13M CWDS (8-13)	N/A	Atypical caudate anatomy in 9/14 CWS. CWS have deficit in cortico-striato-thlamo-cortical network.

Study	Method	Sample	Task	Main Finding height
Weber-Fox et al. (2013)	EEG	20M 7F CWS (3-6) 18M 9F CWDS (3-6)	Listen to grammatically correct sentences and sentences that contained either a semantic or syntactic violation	Longer peak latencies for the N400 component; syntactic violations generate negativity between 150-350ms; CWNS exhibited significant P600 in LH but CWS exhibited significant P600 in RH
Sowman et al. (2014)	MEG	10M 2F CWS (3-5) 10M 2F CWDS (2-6)	Picture Naming	No difference in laterality between CWS and CWDS
Chang et al. (2015)	MRI (DTI)	26M 19F CWS (3-10) 22M 20F CWDS (3-10	N/A	CWS exhibit reduced fractional anisotropy in white matter tracts connecting auditory and motor regions of the brain and those that support timing control.
Usler and Weber-Fox (2015)	EEG	8M 3F pCWS (6-8) 9M 2F rCWS (6-8) 8M 1F CWDS (6-8)	Listen to english or jabberwocky sentences that were either normal or contained a semantic violation	Whereas both CWDS and recovered CWS exhibit a p600 to phrase structure violations in jabberwocky sentences, pCWS do not.

Appendix C.

Table of Neuroimaging Studies on both CWS and AWS

Study	Method	Sample	Task	Main Finding height
Watkins et al. (2008)	fMRI and DTI	12M 5F PWS (14-27) 8M 5F PWDS (14-27)	Read sentences aloud (presented visually) vs. viewing a row of X's with normal, delayed or frequency shifted feedback	fMRI: Irrespective of feedback condition, PWS showed underactivity in the ventral premotor regions. This was accompanied by reductions in fractional anisotropy in the same areas.
Xuan et al. (2012)	fMRI	44M PWS (17-37) 46M PWDS (17-37)	RSFC (eyes closed)	AWS showed increased ALFF in left brain areas related to speech motor and auditory functions. AWS showed decreased ALFF in the bilateral non speech motor areas
Connally et al. (2014)	MRI (DTI)	21M 8F PWS 23M 14F PWDS (14-45)	N/A.	AWS have reduced fractional anisotropy in the arcuate fasciculus More severe dysfluency correlates with reduced white matter in angular gyrus.
Liu et al. (2014)	fMRI	29M 17F PWS (5-51) 33M 19F PWDS (6-50)	Simon Spatial Incompatibility Task.	On incongruent trials, AWS showed stronger activation in the cingulate cortex, left prefrontal cortex, right medial frontal cortex. Activation in anterior cingulate cortex correlated with stuttering severity. Inadequate readiness to execute motor response
Tahaei et al. (2014)	EEG	21M 4F PWS (16-35) 21M 4F PWDS (16-35)	Auditory brainstem responses to speech sounds	AWS have increased latencies for the onset and offset waves of V, A and O to speech ABR. AWS showed deficient timing in early neural response to speech sounds consistent with temporal processing deficits.
Beal et al. (2015)	MRI (VBM)	55 PWS (55-61) 61M PWDS (6-48)	N/A	In PWS only the left pars opercularis exhibited a different developmental trajectory in grey matter with age (None of the 30 other brain regions did).

Appendix D.

Publications

frontiers in
HUMAN NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
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Behavioral and multimodal neuroimaging evidence for a deficit in brain timing networks in stuttering: a hypothesis and theory

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The fluent production of speech requires accurately timed movements. In this article, we propose that a deficit in brain timing networks is one of the core neurophysiological deficits in stuttering. We first discuss the experimental evidence supporting the involvement of the basal ganglia and supplementary motor area (SMA) in stuttering and the involvement of the cerebellum as a possible mechanism for compensating for the neural deficits that underlie stuttering. Next, we outline the involvement of the right inferior frontal gyrus (IFG) as another putative compensatory locus in stuttering and suggest a role for this structure in an expanded core timing-network. Subsequently, we review behavioral studies of timing in people who stutter and examine their behavioral performance as compared to people who do not stutter. Finally, we highlight challenges to existing research and provide avenues for future research with specific hypotheses.

Keywords: stuttering, rhythm, tapping, speech, basal ganglia, cerebellum, timing

THEORIES OF STUTTERING

According to the World Health Organisation (2010, para. F98.5), stuttering is "speech that is characterized by the frequent repetitions or prolongation of sounds or syllables or words, or by frequent hesitations or pauses that disrupt the rhythmic flow of speech." Repetitions typically consist of a repetition of part of a word, a whole word or a phrase (e.g., re... re... re... repetitions). Prolongations consist of a lengthening of the sounds within a word (e.g., prrrrrrrolongations). Complete interruption to the flow of speech, known as "blocking" is also a common symptom of stuttering. Blocks are where there is a length of time where no form of speech is produced either within words [e.g., block-(pause)-ing] or between words. In most cases, stuttering emerges between 2 and 5 years of age, around the time children start preschool. Stuttering has a prevalence of around 5% in early childhood but due to the fact that many children recover spontaneously, the prevalence across the general population is closer to 1% (Yairi and Ambrose, 2013). This percentage of stutterers who do not recover generally experience poorer social, emotional and mental health (Craig et al., 2009; Iverach et al., 2009) and elicit negative reactions from others (Langevin et al., 2010). Stuttering is also associated with secondary or associated signs that include facial grimaces, forced effort and eye-blinks (Conture and Kelly, 1991; Riva-Posse et al., 2008). These secondary signs further impair the ability to communicate effectively and exacerbate the problems that result from the primary symptoms. Importantly, such secondary signs imply that stuttering is not solely confined to the domain of speech but rather a disorder of motor control that manifests primarily in the domain of speech because of the extreme timing and sequencing demands required for that function. Moreover, while difficult, it is not impossible to detect differences related to stuttering in the manual domain (e.g., Max et al., 2003; Ambrose, 2004).

Packman (2012) argues that the necessary condition for stuttering, i.e., the one thing each person who stutters must possess, is a neural anomaly that weakens the integrity of the speech motor system. In this weakened state, the speech motor system is rendered more susceptible to breakdown when various features of the spoken language place increasing demand on the system (Packman, 2012). The point at which stuttering is triggered is modulated according to individual and environmental factors such as levels of physiological arousal. Here we take the view that the necessary condition for stuttering (which unless otherwise specified is used to refer specifically to developmental stuttering) is the presence of a neural anomaly in timing.

The following account proposes the hypothesis that the core disorder of stuttering is a deficit in brain timing-networks. This article is not an exhaustive review of the literature on stuttering

Abbreviations: BG, Basal ganglia; CB, Cerebellum; CTC, Cerebellar-thalamo-cortical; CWDS, Children who do not stutter; CWS, Children who stutter; ETN, External timing network; fMRI, Functional magnetic resonance imaging; IFG, Inferior frontal gyrus; ITN, Internal timing network; MEG, Magnetoencephalography; PD, Parkinson's disease; PET, Positron emission tomography; PMC, Premotor cortex; PWDS, People who do not stutter; PWS, People who stutter; SMA, Supplementary motor area; STC, Striato-thalamo-cortical; STG, Superior temporal gyrus; TMS, Transcranial magnetic stimulation; VBM, Voxel based morphometry.

or the arguments surrounding the cause of the disorder, but rather a hypothesis as to one of the possible causes of stuttering. The proposal that timing is important for speech (see Lashley, 1951; Martin, 1972; Strait et al., 2011) and even speech disorders like specific language impairment (Tallal et al., 1993) dyslexia (Goswami, 2011) or indeed stuttering (Alm, 2004, 2010) is not new. In the later case, the idea that stuttering relates to a deficit of timing follows from the observation that regular external stimulation temporarily alleviates stuttering (see for a revision, Alm, 2004; Snyder et al., 2009). The novel aspect of this article is that it expands on previous research suggesting that dysfunction within a brain network that supports internal timing [comprised of the basal ganglia (BG) and the supplementary motor area (SMA)] is causing stuttering and that a secondary system which utilizes external timing cues to sequence movements [comprised of the cerebellum (CB), the premotor cortex (PMC) and the right inferior frontal gyrus (IFG)] is compensating for stuttering. Specifically, we propose that an internal timing network (ITN), largely equivalent to the "medial system" proposed by Goldberg (1985) is involved in internally timed movement (movement performed in the absence of external timing cues) and is causally related to stuttering. We further propose that an external timing network (ETN), largely equivalent to the "lateral system" proposed by Goldberg (1985), with the addition of the right IFG, is involved in externally timed movement (movement performed in the presence of external timing cues) and provides a substrate for timing compensation in stuttering. Importantly, we are not suggesting that neural deficits in structures underlying timing is the sole cause of stuttering, but rather one of many possible deficits that could lead to stuttering. In this section, we first present multimodal neuroimaging evidence for the possible causal involvement of ITN in stuttering before moving on to discuss putative compensatory roles of the ETN.

There is ongoing debate as to whether some brain regions are specifically dedicated to processing time or whether the capacity to process time is intrinsic to each region of the brain directly through the activation of sensory processes (for review see Ivry and Schlerf, 2008). There already exist reviews outlining the cognitive and neural architecture proposed for how we represent a sense of time (e.g., Buhusi and Meck, 2005), how different sensory networks interact with core timing networks across different tasks (e.g., Merchant et al., 2013) as well as evidence for common timing mechanisms across manual and oral movements (e.g., Franz et al., 1992). While the questions of how and where time is processed in the brain are of considerable practical and theoretical interest, such a discussion is outside the scope of this article. Here we argue that the ETN is primarily active when an individual is timing their movement to an external rhythm and that it is particularly active during early exposure to rhythm or when the rhythm is difficult and is not easily internalized. In contrast to this, the ITN is primarily active when an individual is making rhythmic motor movements that are not specifically timed to an external stimulus. Importantly, the two systems can be active simultaneously such as when an individual is pacing their movements to an external stimulus and is internalizing that rhythm. Practically, this means that results of functional magnetic resonance imaging (fMRI) studies may show no difference in brain activation between conditions that supposedly bias internally or externally-timed movements; however, disruption of these systems via inhibitory transcranial magnetic stimulation (TMS) should yield selective interference in behavioral performance. What follows is a brief overview of studies supporting a dissociation between the ITN and the ETN in timing tasks.

There is strong support for the involvement of the ITN during timing tasks from a number of fMRI, magnetoencephalography (MEG), lesion and TMS studies. For example, a recent fMRI study has found that the BG and the SMA tend to be active when movements are internally as opposed to being externally timed (Coull et al., 2013). Similarly, it has been shown using finger tapping tasks, that the BG and the SMA are active during the continuation phase (no external pacing stimulus, hence an internally-timed process) but not the synchronization phase (with external pacing, hence externally-timed) of the task (Rao et al., 1997). In particular, the BG are more active during the performance or tracking of simple rhythms, i.e., those that are easier to internalize, compared to complex rhythms (Grahn and Rowe, 2009, 2013; Geiser et al., 2012). The fact that fMRI studies show an overlap of neural activity during synchronization and continuation tapping (e.g., Jäncke et al., 2000; Jantzen et al., 2004) provides little support for a functional distinction between brain networks supporting internal and external timing; however, evidence from lesion and TMS does support such a dissociation between the INT and the ETN and their respective functions. Studies show that individuals with bilateral lesions to the BG perform poorly on the continuation phase of the finger-tapping task (Coslett et al., 2010) and are also poor at adjusting to accelerations and decelerations in tempo (Schwartze et al., 2011). Disruption of the SMA by inhibitory TMS impairs accuracy of continuation tapping whilst leaving the accuracy of synchronization tapping intact (Halsband et al., 1993).

There is also evidence for the involvement of CB and the PMC in the ETN. Inhibitory TMS of the CB has been shown to disrupt synchronization to auditory (Del Olmo et al., 2007) and visual pacing (Theoret et al., 2001; Koch et al., 2007). This disruption appears to be selective because lesions to the CB do not affect performance during the continuation phase of the finger-tapping task (Spencer et al., 2003). Likewise, a number of studies show that inhibitory TMS of the left PMC disrupts the synchronization tapping (Pollok et al., 2008; Bijsterbosch et al., 2011) and that this effect is specific to external pacing, as no effect of TMS is observed on continuation tapping (Del Olmo et al., 2007) or when tapping in the presence of, but not in time with, a scrambled beat (Kornysheva and Schubotz, 2011). Taken together, there indeed appears to be a functional dissociation of the ITN and the ETN in healthy adults. We now turn to neuroimaging studies to demonstrate how these systems are impaired in people who stutter.

NEUROIMAGING STUDIES OF THE INTERNAL TIMING NETWORK IN PWS

A number of neuroimaging studies implicate the BG or components thereof in the etiology of stuttering. For example, when comparing the fluent and dysfluent speech of people who stutter (PWS) to people who do not stutter (PWDS), Wu et al. (1995) found that PWS exhibited less activity in the caudate during both

dysfluent speech and fluent speech. This lowered activity was suggested to be a trait marker for stuttering. The BG has also been related to the most typical symptoms of stuttering at an individual level (Jiang et al., 2012). These authors elicited stuttering during a sentence completion task and classified repetitions, pauses and prolongations as being either least typical or most typical of stuttering based on patterns of haemodynamic responses. Jiang et al. (2012) found that one of the activation patterns contributing to this separation of most and least typical symptoms was a reduction in BG activation. Although the aforementioned studies provide a correlative link between the putative ITN and stuttering, they do not unambiguously support the notion that the ITN *causes* stuttering. Because those studies were conducted mainly in adults, and stuttering is a disorder that appears in childhood, it can therefore be hard to determine whether anomalous BG activations observed in PWS are related to the cause of stuttering or are compensations for it.

In contrast, structural and functional abnormalities in children who stutter (CWS) are likely to be more indicative of the causative agents in stuttering because children have not had as much time to adapt to stuttering as adults. Chang and Zhu (2013), examined functional connectivity in CWS and children who do not stutter (CWDS) aged 3–9 and found reduced levels of connectivity between the putamen and the SMA, superior temporal gyrus (STG) and CB and similarly between the SMA and the putamen, STG and CB. Chang and Zhu (2013) concluded that CWS exhibited reduced activity in areas responsible for self-paced movement as compared to CWDS. Similarly, a recent voxel based morphometry (VBM) study conducted in CWS, found less gray matter volume in the bilateral inferior frontal gyri and the left putamen but more gray matter volume in the right rolandic operculum and the right STG relative to CWDS (Beal et al., 2013). In another study, Foundas et al. (2013) measured the volume of the caudate in right-handed boys who stutter and compared them to right-handed boys who did not stutter. They found that male CWS exhibited significantly less volume in the right caudate as compared to male CWDS. These studies suggest that even at a very young age, CWS exhibit abnormalities in structure and connectivity in the ITN. A recent MEG study examined lateralization of brain functions in preschool CWS and CWDS during a picture-naming task (Sowman et al., 2014). These authors found that speech was strongly left lateralized in both groups. Although not explicitly focusing on the ITN, this study demonstrates that much of the abnormal activation observed in the cortical right hemisphere in adults is the result of years of compensation for stuttering rather than being causally related to it. Moreover, that there were no differences between CWS and CWDS in cortical activations further hints at the possibility that stuttering is caused by deficiencies in subcortical regions. Overall, these studies provide strong support for viewing stuttering as a disorder of the BG. Since the BG seems responsible for internal timing of movement, they provide indirect support that stuttering is a disorder of internally timed movement.

To implicate the ITN in stuttering, structural or functional abnormalities should be evident in these structures in both children and adults who stutter and the neural deficit necessary to cause stuttering should be present irrespective of whether or not a subject is performing a task. Ingham et al. (2012) examined speech during oral reading and monologs as well as during a rest condition and found that PWS were different to PWDS in both the medial (ITN) and lateral (ETN) systems proposed by Alm (2004). PWS had significantly more activity in the BG (including the left putamen) during an eyes closed rest condition but significantly less activity during speaking conditions. This was thought to result in difficulties in performing fine-grained movement that may extend to speech and explain the fact that other studies observed increased activation of these regions in speech conditions like oral reading and monolog. More specifically though, if it is the case that the BG are overactive during rest and not just underactive during speech, it would indicate abnormalities in stuttering are not solely confined to speech. That is to say, the problem spans a number of domains because there are functional differences in neural activation occurring in the absence of speech.

If abnormalities of the ITN are causally related to stuttering, then it could be expected that effective speech therapy should produce measurable changes in the neural activity of these structures rather than in the areas compensating for stuttering. To this end, Giraud et al. (2008) examined neural activity using fMRI before and after speech therapy in a group of PWS. Therapy consisted of 3 weeks of undergoing an inpatient program focusing on biofeedback for syllable prolongation, soft voice onset and smooth sound transition. The researchers found that activity in the caudate positively correlated with stuttering severity before speech therapy but not after. Since the caudate was positively correlated with severity rather than negatively correlated with it, the speech therapy appeared to target causal rather than compensatory regions.

Similarly, if the ITN is related to stuttering this will not only be reflected in measures of neural activity but also in terms of the connections within the ITN. Lu et al. (2010) used structural equation modeling to compare causal relationships and function in the ITN in PWS and PWDS during a picture-naming task. Although there were no significant differences between stuttering and non-stuttering speakers in the output of the SMA to the BG, there were significant differences between the groups in the output of the BG to the SMA. More specifically, whereas PWDS showed a strong negative projection from the BG to the pre-SMA, PWS showed a positive projection from the BG to the pre-SMA Lu et al. (2010) interpreted their finding of abnormal output of the BG to the SMA as reflecting the difficulties PWS have in updating the timing and sequencing of movement. Interestingly, like Lu et al. (2010), a number of other studies have also shown altered patterns of activity in the SMA in relation to the perception and planning of speech in stuttering (Chang et al., 2009, 2011). Taken together, these findings, are consistent with the notion that stuttering is the result of dysfunctional processes that engage core structures within the proposed ITN: the BG and the SMA.

LESION STUDIES OF THE ITN IN PWS

If dysfunction in the ITN is thought to cause stuttering, then it follows that damage to these regions may result in stuttering. When stuttering develops following a lesion to the brain it is known as acquired or neurogenic stuttering (for review see Lundgren et al., 2010). There is evidence that damage to the ITN results in stuttering. For example a recent study by Tani and Sakai (2011) examining five patients with BG lesions (two with

bilateral putamen lesions, two patients with bilateral BG lesions and one patient with a left putamenal lesion) but without aphasia, found that they exhibited dysfluencies such as syllable repetitions, part word repetitions and frequent blocks. Importantly, these patients' symptoms mimicked the characteristics of developmental stuttering in that almost all stuttering occurred on the initial syllable of a word. In a number of case studies, Ciabarra et al. (2000) describe a right-handed woman with a left BG lesion, and a woman with a left corona radiata, putamenal and subinsular infarct who both stuttered. Similarly, a number of different case studies have reported the onset of stuttering following damage to the SMA (Alexander et al., 1987; Ackermann et al., 1996; Chung et al., 2004). Furthermore, direct electrical stimulation of the SMA has also been shown to induce stuttering (Penfield and Welch, 1951). These findings are consistent with the notion that damage to the SMA can cause speech disorders and that the SMA is linked with the rhythmic control of speech (Jonas, 1981). This and other works have prompted investigation into the role of the SMA in rhythmic movements of the mouth (MacNeilage and Davis, 2001) as well as dissociations between the pre-SMA and the SMA-proper in rhythmic timing (Schwartze et al., 2012).

NEUROIMAGING STUDIES OF THE ETN SYSTEM IN PWS

There are studies hinting that deficits to the ITN are causing stuttering, but what proof is there that the ETN is recruited to compensate for this? To answer this question, we turn to fMRI studies of PWS. Braun et al. (1997) found the CB to be overactive in PWS during stuttered and fluent speech and it has been suggested that this is a compensatory mechanism for stuttering (see also Alm, 2004). In a meta-analysis of PWS, Brown et al. (2005) identified three neural signatures of stuttering. These neural signatures were the absence of auditory activation bilaterally, the over-activation of the right IFG and the over-activation of the CB. These findings have since been partially replicated by Lu et al. (2010) who found over-activation of the right IFG and the CB (but not the absence of bilateral auditory activation) and interpreted them as compensating for stuttering. Ingham et al. (2012) examined speech during oral reading and monologs as well as rest, finding that PWS exhibited increased cerebellar activity which was negatively associated with stuttering, indicating that the ETN may indeed be compensating for the ITN. A similar study, examined resting state functional connectivity of PWS before and after speech therapy in stuttering and non-stuttering adults (Lu et al., 2012). These authors found increased resting-state-functional-connectivity between the midline CB and a network of regions (comprised of the medial frontal gyrus, the SMA and the left IFG) at rest for PWS relative to PWDS. For the PWS who received intervention as compared to the PWS who did not receive intervention (and PWDS), the resting-state-functional-connectivity in the midline CB returned to normal levels and was correlated with an increase in fluency. As such, Lu et al. (2012) suggested the CB was likely compensating in stuttering. In addition to these, other studies have associated the CB with compensatory activation in PWS (e.g., De Nil et al., 2008; Watkins et al., 2008).

While there is overlap in the neural structures responsible for external timing and compensation for stuttering, it does not automatically follow that the ETN is compensating for deficits in internal timing in PWS. However, there is fMRI evidence showing that the CB and the right IFG specifically compensate for deficits in the BG with respect to timing tasks in those who have Parkinson's Disease (PD). For example, Jahanshahi et al. (2010), investigated the differences in neural activation between PD patients and controls in and the synchronization continuation task. They also examined the effect of administering apomorphine (a non-selective dopamine agonist) on neural activation in the PD patients. Results showed that for healthy controls synchronization and continuation tapping (relative to a control reaction time task) was associated with significantly greater activation in the nucleus accumbens and caudate, a pattern not found in PD patients. In contrast, individuals with PD showed greater activation in the bilateral cerebellar hemispheres, right thalamus and left midbrain during both phases of finger tapping. Administration of apomorphine to the PD patients appeared to normalize activity, both increasing the connectivity between the caudate and putamen and frontal regions as well as decreasing activity in the CB. Thus, the authors suggested that increased cerebellar activation was likely compensating for the impaired functioning of the BG. Sen et al. (2010) found increased cerebellar-thalamo-coritical (CTC) activation as PD progressed, perhaps indicating an increasing need to compensate for loss of function in the striato-thalamo-cortical networks (STC). This increase was only observed during continuation tapping and was not evident during synchronization tapping suggesting that the CTC (i.e., the ETN) was compensating for the STC (i.e., the ITN). The dissociation between the ITN and the ETN may seem problematic given both the CB (part of the ETN) and the SMA (part of the ITN) are thought to compensate for deficits in the BG during self initiated hand movements in the early stages of PD (Eckert et al., 2006). Nevertheless, this could suggest that part of the ITN (the SMA) may still be able to compensate for deficits in other parts of the ITN (the BG) when degeneration is not particularly severe.

COMPENSATION BY THE RIGHT IFG IN STUTTERING

An increasing number of studies have reported anomalous activation of the right IFG in a variety of speech tasks (e.g., Fox et al., 1996; Brown et al., 2005; Sowman et al., 2012) in PWS. Several studies found that increases in right IFG activation during overt reading (Preibisch et al., 2003; Lu et al., 2010) that were positively correlated with speech fluency in PWS and thought to be a non-specific compensatory mechanism because the activation was not specifically related to speech production. Examining the effect of external auditory pacing on the speech of PWS Toyomura et al. (2011) found that, relative to a PWDS, the PWS showed more activation in the right IFG (along with bilateral auditory cortices) during both choral speaking and when speaking in time with an isochronous metronome. There are also reports of increased right frontal connections in adults who began stuttering as children (i.e., developmental stuttering) relative to adults who began stuttering later in life following a psychological trigger and without evidence of brain injury (Chang et al., 2010). This evidence suggests that the longer a PWS has been compensating for their stuttering, the greater the activity in the right IFG.

It is worth noting that Goldberg's formulation of the lateral system (upon which the ETN partially maps) does not contain the

right IFG. Why then should right IFG be considered a part of an ETN that compensates for a dysfunctional ITN in stuttering? This question is particularly relevant when considering that the simplest explanation for right IFG involvement in stuttering is that it compensates for deficits in the left IFG (see Kell et al., 2009). Kell et al. (2009) associate the left IFG with processing of rhythm and sensorimotor feedback and it is possible that the right IFG may perform a similar function. Recently, the right IFG has been recognized as part of a "core timing network" (Wiener et al., 2010) that is recognized to be strongly connected both functionally and structurally to the ITN (Kung et al., 2013; Brittain and Brown, 2014). In particular, the right IFG may only become active when a task is more demanding. That is to say, the difficulty of compensating for deficits in internal timing by external timing regions might account for why there was over-activation of only the CB during speech, but not the right IFG during rest in PWS (Lu et al., 2012). A second, though not mutually exclusive explanation is that while the CB is able to compensate for timing deficits, its ability to do so is limited. This is evident in the case of individuals with PD where behavioral performance worsened despite increases in compensatory activation in the CB (Sen et al., 2010). A similarly limited ability of the cerebellar systems to compensate for deficits in timing may be occurring in PWS as evidenced by the reduced integrity of cerebellar tracts in both the left and the right hemispheres (Connally et al., 2013). Since the ETN has a limited capacity to compensate for deficits in the ITN, the assistance of the right IFG may be required to maintain normal timing functions. A third possible explanation is that the model proposed by Goldberg (1985) (where the ETN is comprised of the CB and the PMC) is incomplete and requires the addition of the right IFG as a secondary part of the system. Importantly, the right IFG is not likely to be the only region that is be compensating for stuttering. There are many other regions like the orbitofrontal cortex that could found to be compensating depending on the task and motor regions involved (see Kell et al., 2009; Sowman et al., 2012). Our contention is that the right IFG forms part of a network that compensates for deficient internal timing.

BEHAVIORAL STUDIES OF TIMING IN PWS

If stuttering is the result of dysfunction in the ITN, and the ITN is important for timing, then it follows that PWS should exhibit deficits in behavioral performance on timing tasks. To this end several groups have found significant differences in asynchrony and variability of tapping between PWS and PWDS. For example, measuring the timing variability of reading sentences or nursery rhymes or tapping, Cooper and Allen (1977) found that PWS were consistently more variable in the length of time it took them to read sentences, paragraphs or nursery rhymes, and in their inter-tap intervals compared to PWDS. Brown et al. (1990) found that PWS were slower and less variable than PWDS at repeating the phrase "ah" and tapping their fingers as at their own pace compared to PWDS, findings they interpreted to represent less flexible timing systems which were more susceptible to breakdown. Similarly, when examining the timing intensity and variability of externally timed speech, Boutsen et al. (2000) showed that although both PWS and PWDS exhibited similar intensities when producing syllables, PWS were significantly more variable in their inter-onset vocalization times (analogous to the inter tap interval in tapping tasks). Additionally, Zelaznik et al. (1997) found that PWS were more variable on bimanual finger tapping (something more demanding than unimanual finger tapping) relative to PWDS. Similarly, Hulstijn et al. (1992) found that on a task which required the coordination of finger tapping and vocal responses (tapping in time with vocalizing the word "pip"), PWS exhibited greater variability than PWDS. More recently, Olander et al. (2010) compared hand-clapping variability in CWS and CWDS. While there was no difference in mean clapping rate, there were significant differences between groups in the variability of the clapping rate. This variability was bimodally distributed, with 60% of CWS showing variability that was greater than the worst performing CWDS. The remaining CWS showed variability in clapping that overlapped with that of the CWDS. Interestingly, this number approximately corresponded to the number of children that spontaneously recover and whose stuttering persists. As a result, the authors suggested that the motor timing deficit may be predictive of recovery from stuttering. Later, Foundas et al. (2013) found that when male CWS were required to tap as fast as possible in a given time period, most were better when tapping with their left rather than right hands as compared to most male CWDS who showed an advantage for their right hand. A recent behavioral study has found robust differences in tapping performance between CWS who stutter compared to CWDS (Falk et al., 2014). In contrast to the CWDS, the CWS not only tapped earlier and were less consistent in tapping, but also failed to improve with age.

However, a number of studies have compared the asynchrony and variability of PWS and PWDS on externally or internally timed vocal or oral motor movements and found similar levels of variance between the groups (e.g., Hulstijn et al., 1992; Melvine et al., 1995). Similar results have been obtained by Zelaznik et al. (1994) who compared PWS and PWDS on externally and internally timed manual responses for isochronous intervals and found that the groups did not differ in behavioral performance. Likewise, Max and Yudman (2003) found PWS and PWDS displayed highly similar levels of asynchrony and variability for finger tapping and producing vocalizations for multiple isochronous intervals. Overall, the behavioral studies investigating the timing abilities of PWS have produced mixed results. While some studies have found differences between PWS and PWDS, many have failed to find differences between groups. From this research, it might seem appropriate to conclude that stuttering is not a disorder of timing and that the links between stuttering and deficits in production of timed limb movements is tenuous at best. One possible explanation is that motor control of limbs and speech is different both centrally and peripherally (Kent, 2000). However if this were indeed the case, then it would be hard to explain why some studies did find significant differences between PWS and PWDS in non-speech motor tasks. Moreover, there is evidence of common timing systems across modalities (Franz et al., 1992) and it has been stressed that the behavioral differences between PWS and PWDS are not confined to the speech production system and instead appear to be generalized deficits (Max et al., 2003). There are other possible explanations for the failure to find behavioral differences between groups which can, in part, be attributed to compensatory neural activity and task difficulty.

TENTATIVE SUGGESTIONS FOR TIMING DEFICITS IN PWS

The substantial number of studies finding no difference in timing behavior in PWS and PWDS is inconsistent with the notion that stuttering could be considered a disorder of timing. How then can we resolve these seemingly paradoxical findings with the consistent observation that neural regions involved in internal timing display anomalous function and structure in stuttering? The absence of a difference at a behavioral level does not imply the absence of differences at a *neural* level. Even a task as simple as tapping a finger or vocalizing to a metronome recruits a complex network of brain regions each with a variety of different functions (Repp and Su, 2013). Moreover, there may be differences at the neural level in the absence of differences at the behavioral level precisely because PWS are compensating for deficits in internal timing. Such a possibility is highlighted by the findings of Neef et al. (2011), who, utilizing inhibitory TMS, showed PWS did not exhibit behavioral differences in timing prior to stimulation but did exhibit behavioral differences subsequent to stimulation. If the suggestion that PWS demonstrate similar behavioral performance as a result of re-organization is plausible, then PWS should exhibit compensatory neural activity in regions associated with external timing of movement that are specifically compensating for deficits in the internal timing of movements. This indeed appears to be the case as both the CB and the right IFG seem to be compensatory regions in stuttering; both appear to be associated with timing, and both may specifically be compensating for deficits in the BG's control of timing tasks. Although speculative, this strongly suggests that the compensatory response to stuttering that occurs during speech is occurring as a result of deficits in the ITN. It perhaps explains why, in some studies at least, PWS have not shown differences in asynchrony (the difference in time between taps and the pacing signal) or variability (in the time between taps) on tapping tasks compared to PWDS. However, any failure to find a difference between these groups may also be attributed to task related effects such as the motoric or temporal complexity.

Many of the behavioral studies investigating timing abilities in PWS employed simple motoric and temporal tasks. Tapping at isochronous intervals is, as a task, relatively easy and this ease may explain a lack of differences in behavioral performance between PWS and PWDS, a problem that may extend to differences in regional brain activation in neuroimaging studies. Imaging data from early research on finger movements shows that the amount of cerebral blood flow to a particular region depends upon the complexity of the task (Shibasaki et al., 1993). Simple tasks are, *ipso facto*, not sufficiently motorically demanding to engage parts of the brain normally employed in more complex tapping tasks and which are impaired in PWS. This principle has been demonstrated experimentally in a number of studies. For example, Zelaznik et al. (1994) failed to find behavioral differences when comparing unimanual tapping performance, but successfully found differences in the same group of stuttering participants when examining bimanual tapping at an isochronous interval (Zelaznik et al., 1997). Similarly, increasing the syntactic complexity of words surrounding a to-be-repeated phrase, decreased speech motor stability for PWS as compared to PWDS (Kleinow and Smith, 2000).

In the same way that increasing the difficulty of the motor movement associated with the task could better reveal differences (should they exist) in behavioral performance and neural activation, so too could placing more strain on the systems governing temporal control of movements. Whereas Webster (1985) failed to find a difference in behavioral performance for PWS during bimanual tapping in a 1:1 ratio (that is one tap of the right hand for every tap of the left hand), Webster (1990) found that PWS took a substantially longer time to tap the required number of times when tapping in a ratio of 2:1 (that is two taps of the left hand for each tap of the right hand) than PWDS. Tapping at an uneven ratio (2:1) places significantly more demand on the neural systems governing timing than does tapping in an even ratio (1:1). This suggests that PWS are much less efficient in coordinating motor output to complex temporal patterns. Similarly, Lewis et al. (2004) demonstrated that parametrically increasing the number of different intervals in a series of tones resulted in a corresponding increase in neural activation in regions associated with timing. These studies show that, increasing the demands on temporal processing is more likely to yield differences in behavior and by extension, in neural activation. This is particularly relevant in the case of speech since speech is rarely perfectly isochronous but rather quasi-periodic (Martin, 1972). Speech contains multiple levels of temporal complexity (Kotz and Schwartze, 2010; Goswami and Leong, 2013) and is therefore substantially more demanding than tapping at an isochronous interval or in a 1:1 ratio. That is to say, differences in the complexity of rhythms required for speech and finger tapping may explain why most timed movements are relatively normal in PWS. Additionally, the timing required for speech control is robust to interference so difficulties in timing movements or speech may only become evident under increased cognitive loads (e.g., Saltuklaroglu et al., 2009). If PWS were compared to PWDS on a tapping task that contained a similar degree of temporal complexity usually required by speech, then clinically meaningful differences in behavior are likely to emerge. While there is a theoretical distinction between motor and temporal complexity, in practice, this distinction may not be so clear. Using near infrared spectroscopy (a means to measure the level of deoxygenated blood from the scalp somewhat analogous to how fMRI measures neural activity) Koenraadt et al. (2013) found that that the two may not be mutually exclusive. Tapping at multiple frequencies activated larger portions of the motor cortex than tapping at single frequencies. The extent to which manipulating motoric and temporal complexity are able to elicit behavioral differences in timing between PWS and PWDS remains to be tested by future research. Yet, even if these tasks are unable to elicit such differences in PWS, future research investigating the overlap between stuttering and timing should consider the use of neuroimaging techniques.

DIRECTIONS FOR FUTURE RESEARCH

There appears to be a vast gap in the stuttering literature particularly with respect to neuroimaging and brain stimulation of timing tasks. In particular, we know of no fMRI or positron emission tomography (PET) studies that specifically examined internally or externally timed movements in PWS using either simple or complex temporal intervals despite the long theoretical

history of an association between deficient timing and stuttering. The timing deficits we propose to exist in PWS are only tentative suggestions and remain to be verified by future research. Our proposal can nevertheless be used to generate a number of testable hypotheses. For example, it could be hypothesized that PWS show impaired behavioral performance and corresponding neural activation in tasks that require the internal timing of movements (the continuation phase of a finger tapping task) as opposed to the external timing of movements (the synchronization phase of a finger tapping task).

Likewise to the best of our knowledge, there are no studies investigating neural oscillations in PWS in response to isochronous or non-isochronous tones either by passive listening, finger tapping or vocalizations. Given the role of neural oscillations in timing (Arnal, 2012), it would be interesting to investigate how they might differ between PWS and PWDS in the context of a timing task. With respect to studies of brain stimulation, no studies have yet examined the effect of distuptive TMS on the right IFG, the SMA or the CB in PWS in a timing task. Although speculative, it might be expected that tapping in time to a metronome (external timing) will be relatively unimpaired because PWS can rely on the CB and premotor cortices much in the same way as non-stuttering adults do. However for self-paced tapping it might be expected that following inhibitory TMS to the right IFG, PWS will be significantly impaired because they cannot rely on either the right IFG or the BG. In contrast, PWDS will be able to rely on the BG, but not the right IFG. The compensatory function of the right IFG in stuttering is biologically plausible in that it forms part of a core timing-network (Wiener et al., 2010), is functionally interconnected with the BG (Kung et al., 2013) and is utilized for the processing of speech rhythm (Geiser et al., 2012).

While this article focused on the neural correlates of the ITN and the ETN during the perception and production of rhythmic movements and stimuli, there are many other tasks that probe these networks. The finger-tapping task is a continuous task that is often conducted in the presence of a regular external stimulus. It is possible that the regular external stimulus reduces behavioral variability and (possibly the associated) neural activity much in the same way that it is able to temporarily induce fluency in PWS. It would therefore be prudent to examine the timing abilities of PWS on tasks that do not contain such regular stimuli or where there is a disruption to the external stimuli. In line with the hypothesis of impaired internal timing and the hypothesized compensatory increases in regions associated with the processing of external timing of movements, it might be expected that PWS are more reliant on external cues. As such it would be interesting to test abilities of PWS to judge whether a "test interval" is longer or shorter than a "reference interval" and how these judgments are influenced by the presence of a "distractor interval" that they must ignore (see Rao et al., 2001). To this end, we know of no studies that have examined temporal judgment deficits in PWS either behaviorally or neurologically. More generally, if it is demonstrated that PWS exhibit deficits in timing, it would be particularly interesting to see if there is any dissociation between these different types of timing tasks or modalities; There may for example, be a dissociation between motor timing or judgment duration or between auditory and visual timing.

CONCLUDING REMARKS

In conclusion, we provide a theoretical framework with which to view stuttering as a disorder of timing. This paper reviews converging evidence from neuroimaging and brain stimulation experiments showing a great degree of overlap between the structures engaged in the internal timing of movements and the regions thought to be causally involved in stuttering. We also provide evidence of overlap between the neural structures engaged in the external timing of movement and link them with compensatory activity in PWS. We further highlight significant gaps in the literature and suggest avenues for further research motivated by this overarching theory. More generally, this article highlights anomalies in the functional activations and the structural anatomy of the areas involved in the processing of time in stuttering, that are linked to the dysfluent production of speech and should motivate further research in the field.

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Beta oscillations, timing, and stuttering

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INTRODUCTION

It has been proposed that one of the causes of stuttering is a deficit in brain timing networks (Alm, 2004; Ludlow and Loucks, 2004; Etchell et al., 2014). In stuttering, there appear to be structural and functional abnormalities in brain areas (such as the basal ganglia and supplementary motor area) that provide the substrate for internal timing (the ability to time movements without an external cue; Alm, 2010; Etchell et al., 2014). There are also structural and functional abnormalities in areas (such the cerebellum and premotor cortex) linked to external timing (the ability to time movements with an external cue), which are thought to represent compensatory plastic changes in stuttering (De Nil et al., 2008; Watkins et al., 2008; Lu et al., 2012). Currently, it remains unknown whether such deficits in internal timing mechanisms in stuttering may be manifest in any measurable neural marker. One possible candidate is oscillatory activity in the beta frequency band.

THE BETA BAND AND INTERNAL TIMING

Neural oscillations in the beta frequency band (15–30 Hz) are classically related to motor activity (see Kilavik et al., 2013 for review): decreasing in power prior to movement and then rebounding once the movement has finished (Pfurtscheller, 1981). Recently there has been considerable interest in the role beta oscillations might play in the brain's ability to represent temporal information because the observed associations between beta band power modulations and the timing of auditory beats (Arnal, 2012; Arnal et al., 2014). These investigations are only in their infancy but have already produced some intriguing observations. For example, Fujioka et al. (2012) used magnetoencephalography (MEG) to measure beta oscillations while subjects passively listened to sounds at regular (390, 585, and 780 ms) and irregular intervals (varying between 390 and 780 ms). Whereas the slope of the decrease in beta power after the onset of sounds was identical across conditions, the rising slope of beta power was maximal prior to the onset of the next expected sound for the regular but not the irregular conditions. The authors concluded that modulations in beta oscillatory activity represented an internalization of predictable intervals between sounds. More recently, Cirelli et al. (2014) replicated these results in an electroencephalography (EEG) study showing a similar pattern of anticipatory beta activity across multiple temporal intervals. Arnal (2012) contends that the beta modulation observed in the Fujioka et al. (2012) study may reflect the motor system generating efference copy signals at the tempo of stimulation. Empirical support for this prediction comes from recent work by Arnal et al. (2014) who showed that correctly judging whether or not a target tone had been delayed in time was associated with greater cortical beta power before the target tone.

There is good evidence to suggest that beta oscillations in the cortex reflect oscillatory activity originating in subcortical structures. Much of our knowledge of beta oscillatory activity in subcortical regions comes from studies in animals or humans with deep brain implants to treat Parkinson's disease (e.g., Levy et al., 2000) because it is not routinely possible to make such invasive recordings in healthy adults. Nevertheless, the pattern of beta desynchronization and resynchronization observed in the cortex during and subsequent to movement can also be observed in the basal ganglia of humans (Brittain and Brown, 2014) and macaques (Courtemanche et al., 2003). MEG experiments indicate the basal ganglia and cortical regions are connected via functional loops (see Jenkinson and Brown, 2011) further suggesting there is a relationship between beta oscillations at different levels of the brain. Consistent with this line of reasoning, Klostermann et al. (2007) reported that in humans, beta band power recorded from the basal ganglia (using depth electrodes) and the scalp (using EEG) during a cued choice reaction time task was correlated in phase and amplitude (measured by magnitude-squared coherence). Likewise, it has been demonstrated experimentally that the cortex and the subthalamic nucleus exhibit beta band amplitude and phase coherence, and it is hypothesized that such an interaction relies on the striatum (Hirschmann et al., 2011).

The relationship between cortical and subcortical beta oscillations, together with the fact that beta oscillations in the motor and auditory cortices are related to internal timing (Fujioka et al., 2012), suggests that beta oscillations in the striatum might also be related to internal timing. Accordingly, Bartolo et al. (2014) examined the role of beta oscillations in timing by recording local field potentials from microelectrodes implanted in the putamen of healthy macaques during

a synchronization and continuation task. This task requires that the macaques tap in time with a beat (the synchronization phase) and that they continue to tap once the beat has been removed (the continuation phase). Whereas the synchronization phase is an index of external timing (due to the presence of an external stimulus), the continuation phase is an index of internal timing (due to the absence of an external stimulus; Teki, 2014). The main finding from the Bartolo et al. (2014) study was that beta activity was strongly biased to the continuation phase as opposed to the synchronization phase of the task indicating that putamenal beta oscillations are tuned to internal rather than external timing of movement.

There is evidence that beta oscillations can be recorded from the striatum during self-paced movements in humans. Intracranial recordings from the putamen of an epileptic patient showed that beta power peaks near the onset of self-paced bimanual finger extensions (Sochurkova and Rektor, 2003). While not focusing directly on beta oscillations, there is evidence from functional neuroimaging to implicate the striatum in internal timing in healthy adults. For example, Grahn and Rowe (2013) demonstrated that the putamen responds to the detection of regularity rather than the detection of beats, suggesting that it is involved in internally paced movement rather than simply the detection of the presence or absence of a beat. The basal ganglia are also more active during subjective judgments of temporal intervals relative to judgments of externally timed intervals (Coull et al., 2013) and the putamen shows greater activity during continuation tapping but not synchronization tapping as compared to rest (Rao et al., 1997). Interestingly, individuals with bilateral lesions to the basal ganglia perform poorly on the continuation but not the synchronization phase of a rhythmic tapping task (Coslett et al., 2010). Such evidence suggests that the putamen is essential for internal timing.

THE BETA BAND AND STUTTERING

What are the implications of these results in the context of stuttering? If indeed stuttering is a disorder of internal timing (Alm, 2004; Etchell et al., 2014), and if beta oscillations in the basal ganglia are involved in internal timing (Bartolo et al., 2014) and/or the cortex (Fujioka et al., 2012; Cirelli et al., 2014) then it follows that stuttering could be a disorder caused by striatal abnormalities that result in abnormal beta power. More specifically, stuttering could be a disorder in which beta power is hypoactive or where the relationship between cortical and subcortical beta power is unstable. That there are exaggerated beta band responses in adults who stutter (AWS; Rastatter et al., 1998) and reduced beta band responses in children who stutter (CWS; Özge et al., 2004) provides some evidence for this contention.

The suggestion that stuttering is a disorder caused by abnormalities of the striatum is consistent with neuroimaging studies of CWS. Investigating differences in brain structure and function of CWS is valuable because they have had much less time to react to stuttering as compared to AWS. Due to the young age of the population, any differences observed between CWS and children who do not stutter (CWDS), are more likely to reflect anomalies related to the cause of stuttering rather than consequences of stuttering (see for review Chang and Zhu, 2013; Etchell et al., 2014; Sowman et al., 2014). The striatum is involved in the articulatory control of speech at different rates (Wildgruber et al., 2001; Riecker et al., 2005, 2006) and in speech rhythm (Fujii and Wan, 2014) and research shows CWS exhibit reduced levels of connectivity between the putamen and several cortical structures including the supplementary motor area, superior temporal gyrus and inferior frontal gyrus (Chang and Zhu, 2013). CWS also have less gray matter in the left putamen (Beal et al., 2013) than CWDS. Interestingly one study reported CWS exhibit reduced levels of beta band activity at rest in the cortex compared to CWDS (Özge et al., 2004).

If abnormal beta power arising from the striatum is causally related to stuttering, then fluency inducing manipulations should normalize beta power. This contention is supported by functional neuroimaging and electrophysiological studies. The finding that putamenal beta band oscillations are biased toward internal timing (Bartolo et al., 2014), together with the fact that the putamen responds to regularity (Grahn and Rowe, 2013) and is known to exhibit beta band oscillations (Sochurkova and Rektor, 2003), suggest that the striatum tracks regular sounds via modulation of beta activity. An fMRI study has shown that AWS exhibit less activation of the basal ganglia during normal speech compared to rest, but that when speaking in time with regular sounds, the level of basal ganglia activation is comparable to adults who do not stutter (AWDS; Toyomura et al., 2011). Given the positive relationship between BOLD activity and beta band responses (Laufs et al., 2003), the normalization of striatal activity may perhaps be accompanied by normalization of beta band activity. Additionally, since regular sounds influence cortical beta power (Fujioka et al., 2012; Cirelli et al., 2014) and cortical beta is associated with subcortical beta oscillations (Klostermann et al., 2007; Jenkinson and Brown, 2011), it is likely that regular sounds also influence beta power in subcortical structures. There is evidence that delayed auditory feedback (DAF), another fluency inducing mechanism, alleviates cortical beta band abnormalities in AWS. Rastatter et al. (1998) used EEG to show that AWS exhibit hyperactivity of the beta band in the cortex when reading aloud. This hyperactivity was markedly reduced by DAF. In the same way that a metronome affected the haemodynamic response in cortical and subcortical structures (Toyomura et al., 2011), DAF might have also affected beta band oscillations in both cortical and subcortical structures. Indeed most fluency inducing mechanisms seem to work by facilitating coupling between auditory and motor systems as well as the putamen (Stager et al., 2004).

It is unclear whether the hyperactivity of the beta band activity in stuttering (Rastatter et al., 1998) reflects causal or compensatory mechanisms. Since the volume of white matter and beta band amplitude increases with age (Uhlhaas et al., 2010) and because the density of the white matter fibers underlying the motor cortex and superior temporal areas were negatively correlated with the severity of stuttering (Cai et al., 2014). It is our opinion that the hyperactive beta oscillations in the cortex reported in Rastatter et al. (1998) may be compensating for *hypoactive* beta oscillations in the basal ganglia. DAF may have normalized the

beta band oscillations in the basal ganglia thereby reducing the need for compensation via hyperactive beta in the cortex. This idea suggests both AWS and CWS should exhibit reduced beta band responses in the putamen when internalizing rhythms. The fact that fluency-inducing mechanisms reduce the hyperactivity of the beta band in the cortex has major implications for stuttering. Firstly, it implies that without regular external stimulation, AWS have abnormal beta oscillations in the cortex and possibly the striatum. Secondly, normalizing compensatory hyperactivity in the cortex as well as temporarily alleviating stuttering implies that DAF may act to normalize hypoactive oscillations in the striatum.

In summary, if stuttering is a disorder of internal timing and internal timing is represented by modulations of oscillatory power within the beta band in the striatum, then it is likely that the cause of stuttering is reflected in abnormal beta band oscillations in the putamen. This is consistent with the structural and functional abnormalities in CWS (Beal et al., 2013; Chang and Zhu, 2013), the notion that beta band oscillations are evident in the putamen (Sochurkova and Rektor, 2003) and that CWS exhibit beta band abnormalities (Özge et al., 2004). The idea that beta oscillations reflect the neural abnormality causing stuttering is further supported by the observation that fluency-inducing mechanisms normalize activity in the putamen (Toyomura et al., 2011) and also beta power in the cortex (Rastatter et al., 1998). Future studies should thoroughly investigate beta oscillations in stuttering.

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A Conceptual Lemon: Theta Burst Stimulation to the Left Anterior Temporal Lobe Untangles Object Representation and Its Canonical Color

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Abstract

■ Object recognition benefits greatly from our knowledge of typical color (e.g., a lemon is usually yellow). Most research on object color knowledge focuses on whether both knowledge and perception of object color recruit the well-established neural substrates of color vision (the V4 complex). Compared with the intensive investigation of the V4 complex, we know little about where and how neural mechanisms beyond V4 contribute to color knowledge. The anterior temporal lobe (ATL) is thought to act as a "hub" that supports semantic memory by integrating different modality-specific contents into a meaningful entity at a supramodal conceptual level, making it a good candidate zone for mediating the mappings between object attributes. Here, we explore whether the ATL is critical for integrating typical color with other object attributes (object shape and name), akin to its role in combining nonperceptual semantic representations. In separate experimental sessions, we applied TMS to disrupt neural processing in the left ATL and a control site (the occipital pole). Participants performed an object naming task that probes color knowledge and elicits a reliable color congruency effect as well as a control quantity naming task that also elicits a cognitive congruency effect but involves no conceptual integration. Critically, ATL stimulation eliminated the otherwise robust color congruency effect but had no impact on the numerical congruency effect, indicating a selective disruption of object color knowledge. Neither color nor numerical congruency effects were affected by stimulation at the control occipital site, ruling out nonspecific effects of cortical stimulation. Our findings suggest that the ATL is involved in the representation of object concepts that include their canonical colors. ■

INTRODUCTION

Conceptual knowledge refers to a crucial aspect of human cognition that enables us to assign meaning to different entities (words, objects, etc.) and further construct an abstract web representing relationships between factual information (e.g., "lemon" denotes an edible fruit with distinct aroma and flavor). Despite decades of research, there is still debate regarding the mechanisms whereby the human brain represents conceptual knowledge. The divergent opinions on this issue can be generally classified into two prominent camps. On one side of the debate are accounts asserting that concepts require mental simulation of bodily experiences and rely upon neural activity occurring in the perceptual and motoric system (Barsalou, 2008; Martin, 2007). This view, often termed "embodied cognition," rejects the idea that concepts can be built upon amodal symbols and propositions. Instead, it posits that concepts are represented by a distributed network of sensorimotor regions, rather than localized to a module acting as the core neural substrate. For instance, the concept of a lemon would involve a constellation of cortical regions processing its yellow color, round shape, and sour taste. On the other side of the debate are accounts proposing that the central component of conceptual knowledge is a representational "hub" that synthesizes various perceptually based fragments (underpinned by sensorimotor regions, which form "spokes") into a meaningful entity (Lambon Ralph & Patterson, 2008; Patterson, Nestor, & Rogers, 2007). This latter position, generally termed the "hub-and-spoke" theory, suggests that the anterior temporal lobes (ATLs) subserve this integrative processing of the "hub." According to this view, a "conceptual lemon" would entail modality-specific areas (spokes) coding sensory attributes and the ATLs (the hub) constructing a supramodal representation that incorporates these features.

Most research addressing the neural basis of conceptual knowledge has focused on the "spokes" that contribute to modality-related content; the function and neural locus of the "hub" remains a matter of speculation (for discussion, see Binder & Desai, 2011). One approach, frequently adopted by proponents of embodied cognition, is to demonstrate using fMRI that the brain areas that underpin perception or action also mediate the neural representation of conceptual knowledge. For example, there has

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been extensive research into whether retrieving color knowledge (e.g., knowing a lemon is yellow) recruits a cortical region primarily responsible for color perception (the V4 complex, which encompasses the fusiform and lingual gyri; see Bartels & Zeki, 2000).

In a seminal neuroimaging study examining the neural correlates for knowing about and perceiving color, Chao and Martin (1999) probed color knowledge by asking participants to generate canonical color names for grayscale objects. The area sensitive to chromatic information was localized using the typical protocol of passively viewing color Mondrians (square patches containing multiple colors). The color knowledge task activated portions of the left lingual gyrus that were 2 cm lateral to but did not overlap with the activation of the left fusiform triggered by color perception. The authors therefore concluded that the neural basis for knowing about color is distinct from that for perceiving color. By contrast, Simmons et al. (2007) reported that a task requiring retrieval of object color knowledge activated a left fusiform region that was also highly responsive to color perception. They interpreted this as a commonality in neural architecture. It is noteworthy, however, that, when identifying the area sensitive to color perception, Simmons et al. used stimuli of the Farnsworth–Munsell hue test (Farnsworth, 1957), a challenging task requiring detection of subtle differences in hue. This task evoked more extensive regional activity in the ventral occipitotemporal cortex than passive viewing of Mondrians, which could increase the likelihood of an overlap in cortical activity.

In more recent research, a number of factors have been suggested to determine whether percepts and concepts of color recruit the same brain regions. For instance, the V4 complex tends to show greater activity when participants retrieve fine- rather than coarse-grained color memories and also when they have a propensity to process information using visualization rather than verbal skills (Hsu, Kraemer, Oliver, Schlichting, & Thompson-Schill, 2011). This implies that the V4 activity observed in conceptual tasks may be driven by both contextual factors (a difficult task prompting mental imagery) and cognitive factors (a tendency to use color imagery), particularly given that color imagery alone can activate V4 (Rich et al., 2006). Such findings together lend some support to the embodied hypothesis by showing that color knowledge activates some ventral occipitotemporal areas in the vicinity of V4. However, "near" is not "same"—whether the core representation of color knowledge shares any common neural mechanisms with color perception remains a matter of debate (Rugg & Thompson-Schill, 2013).

Considerably less is known about whether brain regions lying beyond the V4 complex contribute to color knowledge and what cognitive operations these areas may underpin. The "hub-and-spoke" theory predicts that, apart from V4 (or its adjacent areas) encoding specifically the chromatic aspect of objects, there is also a hub that unifies color with other sensory attributes and linguistic labels into a supramodal concept (Patterson et al., 2007). Patient research provides hints that the ATL would be a good candidate zone coding supramodal representation. Atrophy of the ATL causes loss of knowledge across various constituent features of an object in the presence of intact ability to perceive those features (Rogers, Patterson, & Graham, 2007; Adlam et al., 2006; Miceli et al., 2001). For instance, Miceli et al. (2001) reported that two patients exhibited severe deficits in object color knowledge but normal color perception. One patient, with damage to the left lingual gyrus but intact ATL, showed a selective loss of object color concept but preserved knowledge for other perceptual and functional properties. The authors argued that lesion of V4 selectively compromised color knowledge. Crucially, the other patient with extensive lesions in bilateral ATLs but spared lingual gyri exhibited widespread deficits in the knowledge for all attributes (color, shape, function, etc.) linked to an object, implicating the ATL "hub" in the conceptual amalgamation of object attributes.

Despite some patient research suggesting a role for the ATL in color knowledge, the picture is not yet clear. In these studies, the damage is not perfectly circumscribed to the ATL. Moreover, fMRI studies have rarely observed ATL activity in response to retrieval of the chromatic memory of objects. This has led to its possible contribution in neurocognitive models of color knowledge being given short shrift. The "failure" to find ATL activation in fMRI research could result from multiple methodological limitations: First, images of the ATL are usually distorted because of field inhomogeneity around the air-filled cavities near the ATL (Devlin et al., 2000). Second, some studies have limited coverage of the temporal lobe because of a restricted field of view during data acquisition. According to a meta-analysis, the inferior section of the ATL tends to get excluded when the researchers use imaging parameters that have a field of view narrower than 15 cm (Visser, Jefferies, & Lambon Ralph, 2010). Third, because the primary aim is often to test whether color knowledge engages the same neural basis of color perception, many studies employ a ROI approach, focusing on the V4 complex (e.g., Hsu, Frankland, & Thompson-Schill, 2011; Hsu, Kraemer, et al., 2011; Simmons et al., 2007). As a consequence, areas outside of the scope of V4, including the ATL, are often not included as ROIs. Thus, it remains unclear whether representing the chromatic aspect of objects at a conceptual level involves the ATL.

The aim of this study was to explore the role of the ATL in the neural representation of color knowledge, contributing to our understanding about how the brain represents a "conceptual object" in general. We used TMS to temporarily disrupt neural processing within the left ATL. TMS allows us to test the causal relationship between a cognitive function and a targeted cortical region in healthy individuals. As most of the patients with ATL lesions have extensive and often bilateral lesions outside the anatomical territory of the ATL (e.g., Adlam et al., 2006; Mummery et al., 2000), TMS in healthy participants

provides a more constrained approach than research of patients (although note that there can be propagation beyond the area stimulated directly). Access to object color knowledge was probed using a naming task in which target objects were presented in their typical or atypical color. Specifically, this task required verbal naming in response to objects with highly diagnostic colors. Object images were presented in either their respective congruent/typical color (e.g., a yellow lemon) or an incongruent/atypical color (e.g., a red lemon). This induced a highly reliable color congruency effect that canonically colored objects are identified faster than atypically colored objects. This task has been used in previous studies of both patients (Miceli et al., 2001) and healthy participants (Bramao, Reis, Petersson, & Faisca, 2011) as an objective measure of object color knowledge.

We applied stimulation targeting the left ATL, which we hypothesize acts as a hub linking object identity with its characteristic color, and a control site, the occipital pole (OP, which is not involved in conceptual knowledge; see Pobric, Jefferies, & Lambon Ralph, 2010b) in separate sessions. Participants performed two tasks: An object naming task that probes color knowledge and elicits a robust color congruency effect (Bramao et al., 2011) and a control numerical task that also results in a reliable congruency effect but involves no conceptual integration (Bush, Whalen, Shin, & Rauch, 2006). The control quantity task required verbal naming of the quantity of an array of Arabic digits. The identity of the digit could be either congruent (e.g., "3 3 3") or incongruent (e.g., "5 5 5") with the required response ("3" in this example). Whereas the color congruency effect was triggered by the conceptual link between objects and colors, the numerical congruency effect was caused by potential conflicts between lexical retrieval of the element versus total number (MacLeod, 1991).

By including both a control site and a control task, we ensured that any effect of ATL stimulation was because of disruption of color knowledge specifically, rather than alternative explanations of nonspecific effects. With the control site, we tested whether disruption to color knowledge resulted solely from ATL stimulation or was potentially a corollary of stimulation at any cortical site. Additionally, with the control task, we tested whether only color congruency would be affected or whether stimulating the ATL would similarly disrupt any type of cognitive congruency or verbal naming response. We adopted off-line continuous theta burst stimulation (cTBS), which uses repetitive magnetic pulses at high frequency and produces a more pronounced and longer-lasting effect than conventional low-frequency stimulation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The longer-lasting impact of cTBS, compared with the relatively brief effect of low-frequency protocols, gave us a better opportunity to assess whether the ATL would be a critical brain region for integrating color with other integral constituents of an object concept.

METHODS

Participants

Eight native speakers of English (three women; mean age = 28 ± 4.5) gave informed consent and participated in the study for monetary compensation. All reported right-handedness and normal color vision and completed safety screening for TMS and MRI before the experiment. None reported any history of neurological disease or mental illness. No participant was on medication or had a history brain injury. This study was reviewed and approved by the Human Research Ethics Committee of Macquarie University.

Design

We used a 2 × 2 × 2 within-participant factorial design, with Stimulation Site (ATL vs. OP), Task (object naming vs. quantity naming), and Congruency (congruent vs. incongruent) as the three repeated-measure factors. In separate sessions, we stimulated one of the two sites, and participants performed both tasks in each session. The order of stimulation sites, as well as that of tasks, was fully counterbalanced across participants. We adopted an off-line stimulation paradigm (i.e., participants received cTBS before the tasks, and performance was probed immediately following stimulation), as this design avoided nonspecific interference on performance because of discomfort, noise, muscle twitches, and so on, relative to on-line paradigms (i.e., applying concomitant stimulation during task execution). This design had two additional advantages over low-frequency (1 Hz) stimulation. First, whereas 1-Hz TMS takes at least 10 min to complete, cTBS requires only 40 sec and hence minimizes possible discomfort during stimulation. Second, compared with the short-lasting effect of 1-Hz TMS (which usually dissipates in 10 min; Sandrini, Umilta, & Rusconi, 2012), cTBS might be able to produce greater inhibitory impact in terms of magnitude and longevity (although note previous demonstrations of the long-lasting effect were based on motor cortex stimulation eliciting motor-evoked potential; see Huang et al., 2005).

Behavioral Tasks

Participants completed two tasks in each experimental session. Each session contained two practice blocks of 12 trials (one block of each task), followed by four experimental blocks of 48 trials (two blocks of each task).

In the object task, participants had to name the object shown in a colored image (Figure 1A). We selected images of 12 objects with strongly associated canonical colors (blueberry, carrot, celery, cherry, corn, eggplant, garlic, kiwifruit, lemon, mushroom, pumpkin, and strawberry). We manipulated the congruency between the display color of each object and its canonical color such that, on congruent trials, objects were presented in the color they

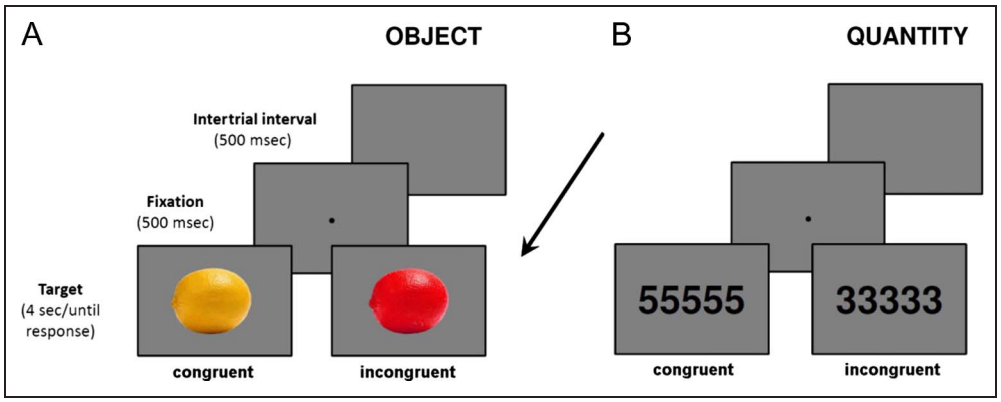

Figure 1. The sequence and time frame of trial events in the (A) object task and (B) quantity task. Target images shown here are example stimuli in both of the congruency conditions. Participants named the object and the amount of digits in the object and quantity task, respectively.

were normally associated with (e.g., a yellow lemon). On incongruent trials, we modified the images using Photoshop so that objects were presented in an atypical color for the object (e.g., a red lemon). The incongruent color was selected from another object's canonical color, avoiding similar or potentially possible colors (e.g., the incongruent color for the lemon was not green; incongruent color for the strawberry was not the cherry red). Thus, each color and object was equally probable in the congruent and incongruent conditions.

In the quantity task (Figure 1B), participants saw an array of Arabic digits (arranged either horizontally or vertically; all elements in a given array were identical) and had to name the quantity of digits. The numbers ranged from one to six. On congruent trials, the identity of the element digit matched the amount of digits in the array. On incongruent trials, the elements and total amount mismatched. The numbers at the amount and element levels as well as the orientation in which they were presented were equiprobable in congruent and incongruent conditions.

For both tasks, each block had equal number of trials in each congruency condition, giving 48 trials per condition, and the two congruency conditions were randomly intermingled within each block.

Each trial began with a black fixation dot on a gray background (RGB triplet = (128, 128, 128); 500 msec), followed by the target image (either an object or a digit array in different blocks) presented for 4 sec or until a response was detected. There was a 500-msec intertrial interval. Participants were asked to name the object (in the object task) or the amount of digits (in the quantity task) into a microphone that registered vocal responses. We asked them to respond as quickly and accurately as possible. In the object task, we emphasized ignoring the color of the object and focusing on its shape/contour/texture to make a response. In the quantity task, we stressed ignoring the constituent digits and concentrating on the quantity of elements. Erroneous responses were recorded manually. A Pentium III computer was used for stimulus presentation and response collection, and the stimuli were displayed on a 17-in. CRT monitor. The experiment was controlled by MATLAB 7.5 with Psychophysics Toolbox (Brainard, 1997; Pelli, 1997).

TMS Procedure

Before the TMS experiments, we obtained high-resolution anatomical T1-weighted MR brain scan for each participant using a Siemens 3T system (Macquarie Medical Imaging, Macquarie University Hospital, Sydney). The individual structural images and the coregistration of cerebral with scalp locations were used to guide the localization of the ATL.

Because of the strong lateralization of language functions to the left hemisphere (Binder, Desai, Graves, & Conant, 2009), we selected the left ATL as the stimulation site and localized its anatomical position on the basis of individual neuroanatomy. In accordance with previous research (Ishibashi, Lambon Ralph, Saito, & Pobric, 2011; Pobric et al., 2010b; Pobric, Lambon Ralph, & Jefferies, 2009; Pobric, Jefferies, & Ralph, 2007), we defined the ATL using anatomical landmarks for each participant: the site 10–15 mm posterior to the temporal pole, along the middle temporal gyrus. The average coordinates of this ATL site in standard space was [−61, −1, −30] across participants, derived using SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) to normalize each participant's ATL in individual brain into the point in the Montreal Neurological Institute (MNI) template (Figure 2). Note that this was performed for comparison with other studies after we completed the experiment and was not used to identify the cortical site or guide the positioning of the TMS coil. After the location of the ATL was pinpointed on each individual's structural scan, the scalp spot directly above this site was identified and marked during the coregistration procedure. Specifically, we used a magnetic tracking system (MiniBird 500, Ascension Tech) and an MRI coregistration software (MRIreg; McCausland Center for Brain Imaging, USA) to identify the scalp location that corresponds the cortical coordinate of the ATL. The control site, OP, was defined as the location of electrode Oz on the international 10–20 system of scalp electrodes. This site fell on a posterior

point on the approximate midline of the occipital cortex and was also marked on the scalp to guide subsequent stimulation, consistent with previous research (e.g., Ishibashi et al., 2011).

cTBS was administered using a Magstim Rapid2 system and a 70-mm figure-of-eight induction coil. We used cTBS in repeating trains of 200 bursts (three magnetic pulses per burst; 50 Hz) with an intertrain interval of 200 msec (5 Hz); the stimulation was applied for 40 sec, with a total number of 600 magnetic pulses (Huang et al., 2005). The stimulation was set at 80% of resting motor threshold (RMT; the minimum stimulation intensity on the motor cortex that causes a visible finger twitch), resulting in an average stimulator output of 38% (range: 34–40%). Before stimulation, we set the experimental stimulus presentation program to standby so that, immediately after the 40-sec cTBS, participants pressed a button to commence the first trial of the behavioral task.

Different lines of inquiry have documented that the scalp-to-cortex distance of the ATL is greater than that of other cortical regions, such as the motor cortex (e.g., Pobric et al., 2007; Stokes et al., 2005). This leads to the possibility that TMS could have less impact at the ATL site because of its distance from the scalp, relative to other areas. As it has been repeatedly demonstrated that RMT is reliably higher than active motor threshold (the minimum intensity that triggers a motor-evoked potential; see Chen et al., 1998; Hess, Mills, & Murray, 1987), we used RMT rather than active motor threshold to circumvent the potential attenuation issue. When testing RMT for each individual, we applied single pulse stimulation to the left primary motor cortex hotspot; the value was defined as the minimum intensity capable of eliciting a visible twitch in the right abductor pollicis muscle on 6 of 10 contiguous trials.

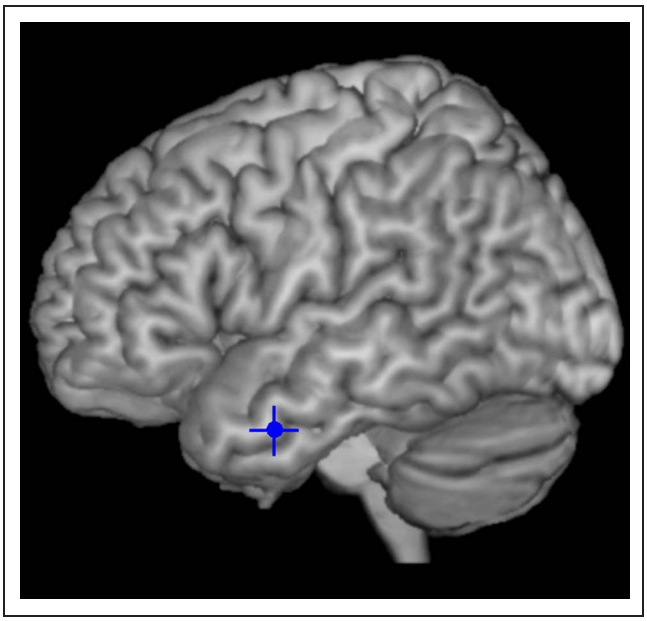

Figure 2. The location of the left ATL on a standardized brain template with the average MNI coordinates [−61, −1, −30].

It has been shown that the behavioral impact of TMS at ATL does not vary with different coil orientations (Pobric, Jefferies, & Lambon Ralph, 2010a; Lambon Ralph, Pobric, & Jefferies, 2009). Thus, we manipulated coil positions to find an angle that minimized facial muscle twitches in each individual. For the ATL, the coil was placed tangentially to the scalp with the handle pointing posteriorly (parallel to the rostral-caudal axis) for six participants and upward (perpendicular to the axis) for the remaining two. For the OP, the coil was always held with the handle pointing upward. The order of stimulation sites was counterbalanced across participants, and the two sessions were separated by at least 72 hr.

RESULTS

After excluding errors (2.6%) and RT outliers (RTs < 100 msec: 1.8%; RTs > 2500 msec: 0.1%) for eight participants, we analyzed the mean RTs of each condition (Figure 3A) with a repeated-measures ANOVA, with the within-participant factors of Site (ATL vs. OP), Task (object vs. quantity), and Congruency (congruent vs. incongruent). The analyses revealed significant main effects of Task, $F(1, 7) = 10.41$, $p = .01$, $\eta^2 = .59$, and Congruency, $F(1, 7) = 64.95$, $p < .001$, $\eta^2 = .90$, and a Task × Congruency interaction, $F(1, 7) = 7.82$, $p = .02$, $\eta^2 = .52$. Importantly, there was a significant three-way interaction between Site, Task, and Congruency, $F(1, 7) = 6.34$, $p = .04$, $\eta^2 = .47$. To identify the source of the three-way interaction, we conducted post hoc pairwise comparisons, testing whether there was a significant congruency effect (incongruent vs. congruent RTs) in each condition. As evident in Figure 3B, stimulation of the control OP site did not affect either the significant color ($p = .003$) or the significant numerical ($p < .001$) congruency effects. Crucially, the numerical effect remained robust after ATL stimulation ($p < .001$), but we no longer see a significant color effect ($p = .13$, *ns*). Although a lack of statistical significance does not necessarily mean "no effect exists," the change from a large significant effect to the substantially smaller and no longer significant difference suggests the key role of ATL in color knowledge.

Furthermore, we then directly tested whether the magnitude of the congruency effect was significantly reduced after ATL stimulation relative to the control OP stimulation. We first derived the difference scores (incongruent minus congruent, indexing the size of the effect) for each condition and participant. These data were then analyzed using repeated-measures ANOVA with within-participant variables of Site (ATL vs. OP) and Task (object vs. quantity). Results showed a significant main effect of Task, $F(1, 7) = 8.15$, $p = .02$, $\eta^2 = .53$, and, pertaining to our main interest, a significant Task × Site interaction, $F(1, 7) = 6.58$, $p = .03$, $\eta^2 = .48$. On the basis of the significant interaction, we performed post hoc tests by Task. Results showed that,

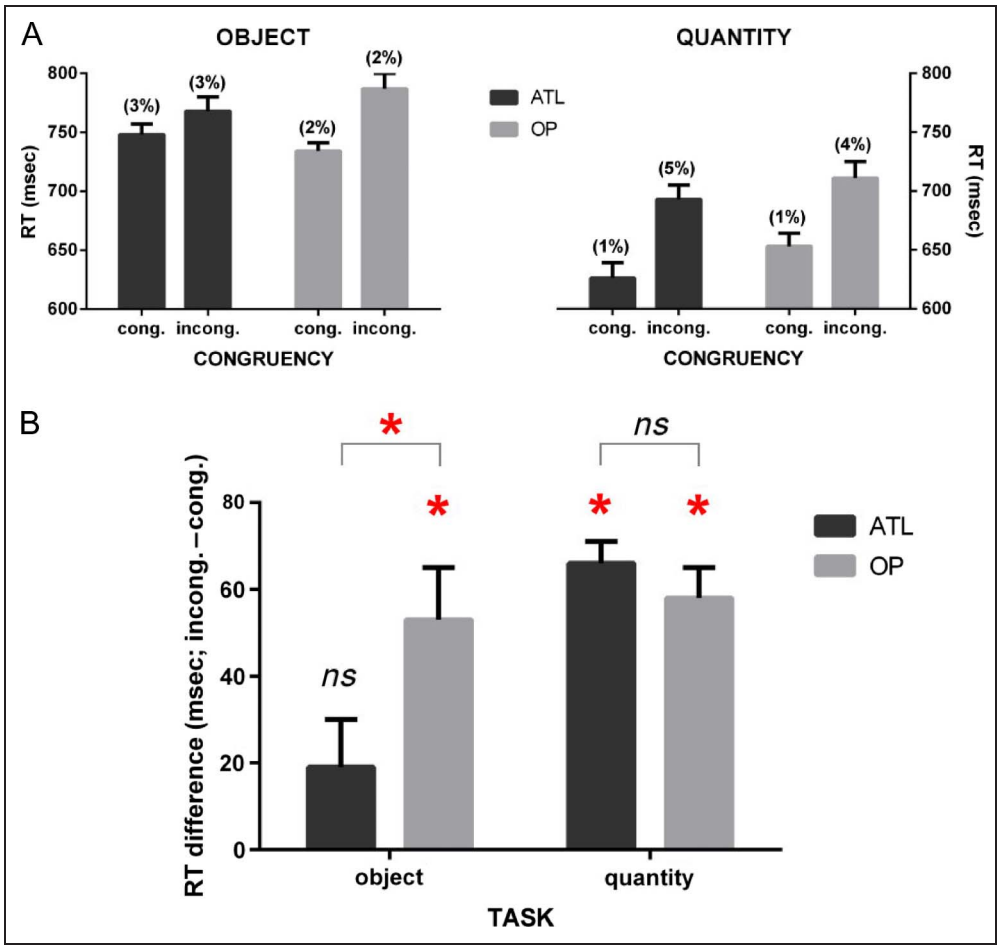

Figure 3. Performance of eight participants on the object and quantity naming tasks. (A) RT as a function of Stimulation Site (ATL vs. OP), Task (object vs. number), and Congruency (congruent vs. incongruent), with the mean error rate (%) of each condition in parentheses. (B) The magnitude of the congruency effects (incongruent − congruent RT) for each task and stimulation site. Error bars represent one repeated-measure *SEM*. An asterisk represents a statistically significant difference in the post hoc comparison. Abbreviations: ATL = anterior temporal lobe stimulation site; OP = occipital pole control site; cong. = congruent; incong. = incongruent.

in the critical object naming task, there was a significant difference in the magnitude of the color effect between the ATL and OP conditions (p = .03, comparing the leftmost two bars in Figure 3B), with the effect being ~2.7 times smaller in the ATL condition (19 msec) than in the OP condition (53 msec). In contrast, there was no difference in the magnitude of the effect on the quantity naming task between the ATL and OP conditions (p = .32, *ns*, the rightmost two bars in Figure 3B). Together, the results demonstrate that ATL stimulation selectively reduced the impact of color knowledge on object recognition and naming.

The analyses on the mean error rates (Figure 3A) only revealed an effect of Congruency, $F(1, 7) = 5.27$, p = .05, η^2 = .43. This is consistent with previous suggestions (e.g., Pobric et al., 2007) that the effect of TMS to the ATL manifests in RTs rather than in errors (as seen in patient research) because the impact of a TMS-elicited "virtual lesion" is more subtle than real brain lesions.

DISCUSSION

The neural basis of object color knowledge is a topic under intensive exploration because it provides important clues as to how the human brain generally integrates sensory information with more abstract knowledge. Most research examines whether color knowledge depends on the V4 complex, a ventral occipitotemporal region specialized for color perception. The status of V4 as the sole neural substrate for representing color is challenged by the observation that some patients with atrophy of the ATL but intact V4 (hence normal color vision) nonetheless exhibit impairments in color knowledge, implying that the neural representation of color knowledge engages areas beyond V4. However, the scope of the atrophy usually extends to areas outside the realm of the ATL, rendering the inference of its neurocognitive function difficult. In this study, we employed cTBS to explore whether the ATL plays a pivotal role in object color knowledge, synthesizing canonical color with other object attributes at a conceptual level. Our results revealed that disrupting the neural processing of the ATL using cTBS eliminated the otherwise robust congruency effect of color knowledge on object naming. By contrast, stimulating the ATL had no impact on the numerical congruency effect in the quantity naming task. This suggests that ATL stimulation did not yield domain-general interference with any congruency-type effect or with giving verbal responses, but instead specifically disrupted conceptual knowledge. Both color and numerical congruency effects remained robust after we stimulated the control OP site, ruling out the possibility that cortical stimulation of any site could

generate nonspecific influences eliminating the color effect. Our findings corroborate previous patient research regarding the potential contribution of the ATL in representing object attributes, mimicking the pattern of cognitive deficits in patients with a mild extent of ATL atrophy (Hoffman, Jones, & Lambon Ralph, 2012). The TMS evidence complements patient and neuroimaging research by directing a virtual lesion at the ATL to enable inference about causality. Taken together, we suggest that the neural processing of color knowledge goes beyond the perceptual analysis of the V4 complex. More importantly, the ATL is engaged in representing object color knowledge, integrating the perceptual and conceptual components of an object to allow successful identification.

As with all TMS studies, we need to add the caveat that our results may be because of disruption of an area connected to the ATL, rather than the ATL itself. With the widespread interconnection of the brain, the impact of neurostimulation does not necessarily stay within the targeted site but may well propagate to other regions with which that area is connected, modulating the neural activity of remote areas (e.g., van Schouwenburg, O'Shea, Mars, Rushworth, & Cools, 2012). Therefore, one possible interpretation of our finding is that the ATL or an unspecified connected area is critical for color knowledge. Given the established role of the V4 complex in color-related processing, could stimulating the ATL interfere with neural processing of V4, thereby abolishing the color effect? If this were the case, we would expect that stimulation of the OP (V1 of the visual cortex) would similarly abolish the color effect, as it is anatomically closer to V4 than is the ATL and hosts multiple color-sensitive subregions that send signals to V4 for further processing (Goddard, Mannion, McDonald, Solomon, & Clifford, 2011; Shapley & Hawken, 2011). Contrary to this possibility, however, our results showed that the color congruency effect remained robust after the stimulation of the OP, making this an unlikely explanation. Moreover, the fact that stimulating the ATL did not affect the control numerical effect is also helpful in showing that cTBS only affects only certain domains of cognitive processing rather than having an "across-the-board" effect. Given the improbability of color knowledge being mediated solely by a single cortical subregion, we favor the view that the ATL is one critical component within a wide network that converts percepts into concepts. To further elucidate the properties of this network, future work could combine TMS and neuroimaging to examine the effects of ATL stimulation on neural activity in remote structures.

Relevant to the discussion laid above, the embodied cognition theory is skeptical of the supramodal hub and postulates instead that object knowledge is represented in a widely distributed manner across modality-based cortices (Martin, 2007). With regard to the neurocognitive function of the ATL, the embodied view suggests that the ATL underlies some abstract concepts devoid of perceptual referents, such as knowledge about social relations (Simmons, Reddish, Bellgowan, & Martin, 2010; Simmons & Martin, 2009). By establishing a causal link between the ATL and the effects of color congruency on object naming, we demonstrate the importance of this area even when the concept pertains to a perceptual aspect of tangible objects. Our results are thus consistent with the "hub-and-spoke" theory (Lambon Ralph & Patterson, 2008; Patterson et al., 2007), which predicts a division of labor between the ATL and modality-specific regions for the neural architecture of color knowledge. The V4 complex ("spoke") specifically contributes to chromatic dimension of object representation (Chao & Martin, 1999). The ATL, as the "hub," fuses different object attributes together to form a supramodal concept that transcends different senses. Thus, when the neural processing of ATL is disrupted, by either disease or TMS, the cognitive capacity to associate typical color with object identity would be severely weakened, despite the patients/participants having intact color perception.

The possibility for impaired color knowledge with intact color perception leads us to speculate that the essence of conceptual knowledge does not rely on embodied experiences alone. This is not to say that the building blocks of concepts are entirely symbolic and propositional. Rather, it seems that sensorimotor representations play a key role especially when a context requires an "instantiation" of bodily experience for retrieval of conceptual pieces (e.g., a question asking whether a cherry is darker in color than a raspberry—answering this question necessitates mental simulation of memorized colors and activates V4; see Rich et al., 2006). In addition to perceptual experiences that provide "raw materials" for concept formation, the conceptual system requires a supramodal representation, possibly coded in a region that receives multimodal inputs like the ATL, to permit coherent "feature-to-concept" mapping. With this supramodal "hub," the operation of the cognitive system is able to transcend constituent perceptual features and extract meaning at a more abstract level (e.g., knowing that candy floss resembles clouds in appearance but is conceptually similar to lollipops, despite it being perceptually distinct). Our interpretation of the contemporary literature and our own finding is consistent with the behavioral deficits observed when the hypothesized supramodal representation breaks down because of a lesion of the ATL (e.g., Hoffman et al., 2012; Lambon Ralph, Sage, Jones, & Mayberry, 2010). For instance, patients with atrophied ATLs but intact perception have been observed to ignore the conceptual relationship between objects and base their judgments heavily on perceptual similarity (Lambon Ralph et al., 2010).

It is worth noting that color knowledge is not the sole object feature that the ATL underpins. A recent neuroimaging study by Peelen and Caramazza (2012) found that, whereas perceptual features of object images were represented by the occipitotemporal regions, locative and motoric properties of objects at conceptual level (e.g., corkscrews are usually found in the kitchen and used

with a rotating action) were coded in the ATL. In line with our finding, the ATL appears to distill information from every sensorimotor channel and to synthesize different properties into a supramodal concept of objects.

Although we used visual stimuli, there is other evidence showing that ATL contributes to conceptual processing whether the input stimuli are presented as images (Pobric et al., 2010a), words (Holland & Lambon Ralph, 2010), ambient sounds (Visser & Lambon Ralph, 2011), or even odors and flavors (Piwnica-Worms, Omar, Hailstone, & Warren, 2010; Luzzi et al., 2007). The modality-independent nature suggests that the "ciphers" coded by ATL for conceptual knowledge are supramodal in nature (although note that it has been suggested that the brain preferentially codes verbal and pictorial knowledge in the left and right ATL, respectively; see Gainotti, 2012).

In conclusion, there has been considerable debate over how the brain represents color knowledge, with most research focusing on the V4 complex. We show, for the first time, that knowing how objects and colors are typically coupled together requires a representational hub mediated by the ATL. We interpret the results in favor of the hub-and-spoke theory where conceptual knowledge can be envisioned as a neural network containing a hub that mediates conceptual integration at an abstract level and multiple spokes that process modality-specific contents.

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Appendix E.

Ethics Approvals

MACQUARIE UNIVERSITY

Research Office
Research Hub, Building C5C East
MACQUARIE UNIVERSITY NSW 2109

Phone **+61 (0)2 9850 8612**
Fax +61 (0)2 9850 4465
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Ethics
Phone **+61 (0)2 9850 6848**
Email ethics.secretariat@vc.mq.edu.au

15 May 2009

Dr Paul Sowman
Macquarie Centre for Cognitive Science
Faculty of Human Sciences

Reference: HE27MAR2009-R06420

Dear Dr Sowman

FINAL APPROVAL

Title of project: Cortical networks that integrate auditory input and speech motor output in human stutterers

Thank you for your recent correspondence. Your response has addressed the issues raised by the Ethics Review Committee (Human Research) and you may now commence your research.

Please note the following standard requirements of approval:

1. Approval will be for a period of twelve (12) months. At the end of this period, if the project has been completed, abandoned, discontinued or not commenced for any reason, you are required to submit a Final Report on the project. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. The Final Report is available at: http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms

2. However, at the end of the 12 month period if the project is still current you should instead submit an application for renewal of the approval if the project has run for less than five (5) years. This form is available at http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report (see Point 1 above) and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

3. Please remember the Committee must be notified of any alteration to the project.

4. You must notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that might affect continued ethical acceptability of the project.

5. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University http://www.research.mq.edu.au/researchers/ethics/human_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide Macquarie University's Research Grants Officer with a copy of this letter as soon as possible. The Research Grants Officer will not inform external funding agencies that you have final approval for your project and funds will not be released until the Research Grants Officer has received a copy of this final approval letter.

Yours sincerely

p.p.

Ms Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

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18 June 2009

Dr Paul Sowman
Macquarie Centre for Cognitive Science
Faculty of Human Sciences

Reference: HE29MAY2009-R06572

Dear Dr Sowman

FINAL APPROVAL

Title of project: Cortical networks that integrate auditory input and speech motor output in young human stutterers

Thank you for your recent correspondence. Your response has addressed the issues raised by the Ethics Review Committee (Human Research) and you may now commence your research.

Please note the following standard requirements of approval:

1. Approval will be for a period of twelve (12) months. At the end of this period, if the project has been completed, abandoned, discontinued or not commenced for any reason, you are required to submit a Final Report on the project. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. The Final Report is available at: http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms

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Yours sincerely

P.P.

Ms Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

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13 June 2014

Dr Paul Sowman
Department of Cognitive Science
Faculty of Human Science
Macquarie University NSW 2109

Dear Dr Sowman,

RE: *Brain networks that integrate auditory input and motor output in human speech*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)) at its meeting on 29 May 2014.

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated March 2014) (the *National Statement*).

Details of this approval are as follows:

Reference No: 5201400596

Approval Date: 13 June 2014

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Macquarie University Ethics Application Form	2.3	July 2013
MQ Participant Information and Consent Form (PICF) entitled *Corticol networks that integrate auditory input and speech motor output in humans*	1	May 2014
Short Protocol entitled *Corticol networks that integrate auditory input and speech motor output in humans*		Received 21/5/2014
Flyer entitled *Stutterers needed for research*	1	Received 21/5/2014
Newspaper Advertisement	1	Received 21/5/2014
Questionnaire for New Stuttering Participants-Adults	1	Received 21/5/2014

This letter constitutes ethical and scientific approval only.

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

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3 July 2014

Dr Paul Sowman
Department of Cognitive Science
Faculty of Human Sciences
MACQUARIE UNIVERSITY NSW 2109

Dear Dr Sowman,

RE: *Cortical networks that integrate auditory input and speech motor output in young human stutterers*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)) at its meeting on 26 June 2014 at which further information was requested to be reviewed by the Ethics Secretariat.

The requested information was received with correspondence on 2 July 2014.

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated March 2014) (the *National Statement*).

Details of this approval are as follows:

Reference No: 5201400680

Approval Date: 2 July 2014

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Macquarie University Human Research Ethics Application Form	2.3	July 2013
Correspondence from Dr Paul Sowman responding to the HREC's feedback.		Received 02/07/2014
MQ Participant Information and Consent Form (PICF) entitled *Cortical networks that integrate auditory input and speech motor output in young human stutterers*	1	June 2014
Questionnaire for New Stuttering Participants-Children	1	02/07/2014

Newspaper Advertisement	1	02/07/2014
Neuronauts Brain Science Club Advertisement	1	02/07/2014
Advertising Flyer	1	02/07/2014
Short Protocol	1	02/07/2014

This letter constitutes ethical and scientific approval only.

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

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The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.