Atypical Neuronal Oscillatory Synchrony of the Auditory Steady State Response in Down Syndrome

by

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B.A., University of Victoria, 2014

Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

in the
Department of Biomedical Physiology and Kinesiology
Faculty of Science

SIMON FRASER UNIVERSITY
Summer 2017

Approval

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Degree: **Master of Science**

Title: **Atypical Neuronal Oscillatory Synchrony of the Auditory Steady State Response in Down Syndrome**

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Abstract

The mechanisms by which the brain coordinates a constant flood of information to provide a unified perception of reality remains poorly understood. Mounting evidence suggests that information integration is closely related to oscillatory activity in the gamma frequency band. Individuals with Down Syndrome (DS) reportedly struggle with higher cognitive processes, but existing knowledge representing the neuronal oscillatory dynamics of the DS brain remains limited. Cortical circuit dysfunction can be probed by the examination of phase coherence of the Auditory Steady State Response (ASSR). Using a measure of phase coherence to assess oscillatory synchrony in the auditory cortices, results show evidence of reduced inter-hemispheric phase locking in the gamma band at the group level (N=12) for DS individuals ($p < 0.01$) compared to control participants. These findings indicate the DS brain does not integrate information as effectively as non-DS individuals do, contributing to a deeper understanding of the neurophysiological correlates of DS symptomology.

Keywords: Down Syndrome; MEG; Gamma; ASSR; Phase Locking; Auditory Cortex

Acknowledgements

I would like to acknowledge the unwavering support of my supervisory committee in the completion of this project, as well as the guidance of my colleagues and friends in both the NeuroTech Lab and Behavioural and Cognitive Neuroscience Institute. I would also like to acknowledge Dr. Larry Roberts, Dr. Arlene Young, Dr. Daniel Bosnyak, Kallista Bell and Careesa Liu for their dedicated work in this study.

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List of Acronyms

AEF	Auditory Evoked Field
AAL	Automatic Anatomical Labelling (Atlas)
AD	Alzheimer's Disease
ASD	Autism Spectrum Disorder
ASSR	Auditory Steady State Response
BOLD	Blood Oxygen Level Dependent
CFC	Cross Frequency Coupling
DS	Down Syndrome
DSRF	Down Syndrome Research Foundation
EEG	Electroencephalography
ERF	Evoked Related Field
ERP	Event Related Potential
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma Aminobutyric Acid
Hz	Hertz
MEG	Magnetoencephalography.
NMDA	N-Methyl-D-Aspartate
PV	Parvalbumin
SQUID	Superconducting Quantum Interference Device
SZ	Schizophrenia

Chapter 1.

Introduction

The recent advancement in brain imaging technologies has led to a vast expansion in the depth of knowledge of how the brain works. The healthy brain can be assessed for regular functioning, and compared to atypical neural activity in clinical populations.

Various imaging modalities measure different aspects of brain function. Neuronal activity can be detected in near real-time using magnetoencephalography (MEG), which detects the small magnetic fields produced by the electrical current of neuronal activity (Cheung, 2012) using highly specialized sensors called Superconducting Quantum Interference Devices (SQUIDs). A prevalent theory behind the mechanism of neuronal communication suggests that neuronal groups oscillate in synchrony, and such coherence binds information within the brain (Fries, 2005). Neuronal oscillations are classified by frequency and measured in hertz (Hz), or the rate of occurrence per second. These classifications represent the frequency bandwidths: delta (1–3 Hz), theta (4–7 Hz), alpha (8–14 Hz), beta (15–30 Hz), and gamma (>30 Hz). Oscillations in different frequency bands have been linked with distinct functions, for example, gamma oscillations have been shown to be relevant for higher cortical processing and to promote perceptual binding of information (Fries, 2009).

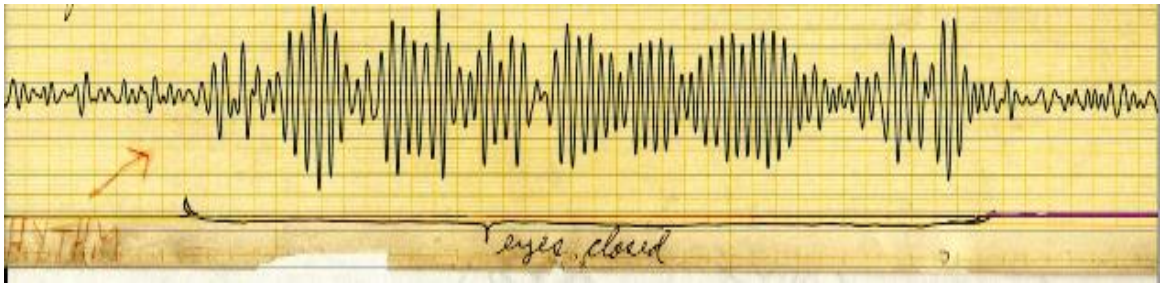

Figure 1.1. The first recorded MEG signal using the SQUID technology used in present day MEG systems. This signal represents the alpha rhythm, in this instance generated by opening and closing the eyes. Copyright 1972 by David Cohen. Adapted with permission.

Auditory stimuli presented at a frequency of 40 Hz elicit a peak in activity (Galambos, Makeig, & Talmachoff, 1981) which can be localized to the primary auditory

cortex (Popescu, Popescu, Chan, Blunt, & Lewine, 2008). Administering an auditory stimulus at this frequency repeatedly suggests evidence of neuronal entrainment (Lehmann, Arias, & Schonwiesner, 2016). Analysis of the auditory steady state response (ASSR) has been used extensively as a measure of hearing loss in clinical practice, but it also has relevant applications as a measure of brain function in clinical populations (e.g. Isomura et al., 2016; Oda et al., 2012).

Down Syndrome (DS) is a genetic disorder with consequences in neurodevelopment. Symptoms of DS include cognitive deficits impacting the individuals ability to work, learn and engage socially. Only limited knowledge of DS is currently available to use in developing a neurophysiological model based on neuronal oscillations of the DS brain. Observed behavioural consequences of DS show some similarity to other neurodevelopmental disorders such as Autism Spectrum Disorder (ASD), that show a potential imbalance in inhibitory and excitatory neurotransmission (Rojas, Becker, & Wilson, 2015). The link between gamma oscillatory activity and information processing suggests that one reason that individuals with DS struggle with cognition might be because of atypical oscillatory neural processing (Engel & Singer, 2001).

Here, we investigated the phase coherence, or the consistency in the phase of an oscillation over time, between left and right auditory cortex in participants with and without DS. Low phase coherence is associated with random neuronal firing patterns, and therefore less synchronous activity (Aydore, Pantazis, & Leahy, 2013). Reduced inter-hemispheric phase locking in response to the ASSR suggests impairment of processes related to long-range communication in the cortex. Given the visible behavioural ramifications of DS, this study speculates the DS brain will show reduced phase locking and spectral power during ASSR stimulation, indicating a neural correlate of difficulties in cognition experienced by DS individuals. This project is novel, as inter-hemispheric phase coherence in regards to the ASSR in DS has not been examined using source-space MEG to date.

Chapter 2.

Background

2.1. Down Syndrome

Down Syndrome is a genetic disorder, characterized by an extra or partial extra chromosome 21 (Lee, Chien, & Hwu, 2016). This genetic abnormality results in developmental challenges, including deficits in cognitive abilities leading to behavioural ramifications. Individuals with DS also experience higher rates of Alzheimer's Disease (AD) (Annus et al., 2017) and heart defects (Derbent & Tokel, 2004; Kidd, 1992) posing a potential challenge to their quality of life. The condition was first identified in the 19th century (Ellis, 2013). At this time individuals with DS typically did not survive beyond their teenage years (Mayo Clinic Staff, 2014), often due to comorbid congenital heart disease and respiratory tract infections (Balarajan, Donnan, & Adelstein, 1982). People with DS were often shut out of society, with little social interactions and medical care. With the progression of society toward the social acceptance of conditions affecting neurodevelopment, more resources continue to become available to DS individuals and their families. Better care for DS individuals has increased their life span in the 21st century to approximately sixty years of age (Bittles, Bower, Hussain, & Glasson, 2007).

Despite an increasing interest in the neurophysiological underpinnings of DS symptoms in recent history, little knowledge has been presented regarding a brain-based understanding of cognitive impairment in DS. Specifically, the DS brain has not been extensively studied in the context of neuronal oscillations; the investigation of the neural dynamics in DS is an ongoing pursuit. With an expansion in the depth of knowledge of DS comes a greater potential for the development of novel therapeutic resources to manage the symptoms.

Existing literature investigating the DS brain reports abnormalities in functional connectivity. Underdeveloped connectivity in long-range connections in the DS brain, based on Blood Oxygen Level Dependent (BOLD) signals have been observed using functional Magnetic Resonance Imaging (fMRI) (Anderson et al., 2013). These results

suggest an impairment of information processing between distant neural regions, contributing to the need to study long-range connectivity in the DS brain.

Electroencephalographic (EEG) research shows delayed processing in response to auditory stimuli in DS individuals (Pekkonen, Osipova, Sauna-Aho, & Arvio, 2007). Sensor space analysis in MEG is consistent in showing delayed processing of auditory stimuli in DS individuals (Roberts et al., 2007). Studies showing aberrant auditory stimuli processing indicate slowed or lessened initial perception of an unattended stimulus (Hillyard, Hink, Schwent, & Picton, 1973), but the effect of a repetitive stimulus such as the ASSR has not been reportedly explored in DS. However, evidence of reduced gamma phase coupling has been observed in response to a voluntary movement task in DS (Virji-Babul et al., 2011), as well as reduction in the power of alpha rhythms (Babiloni et al., 2010), suggesting altered oscillatory dynamics in DS.

Structural abnormalities have been observed in the DS brain similar to AD, as chromosome 21 is implicated in neurodegenerative processes (Lott, Head, Doran, & Busciglio, 2006). Individuals in the early stages of AD also experience atypical processing of the ASSR (Osipova, Pekkonen, & Ahveninen, 2006) which may indicate a relationship to accelerated loss of cortical volume seen in both DS and AD. Mouse models of DS report reduced sensitivity of N-Methyl-D-Aspartate (NMDA) receptors (Kleschevnikov et al., 2004), supporting the theory of imbalance in excitatory and inhibitory neurotransmission in conditions affecting neurodevelopment, as NMDA receptors are an integral contributor to excitatory activity in the brain.

The full extent of genetic influence on the manifestation of neurological DS symptoms is not fully understood. Evidence suggests an imbalance of individual genes affects expression of chromosome 21, resulting in phenotypical anomalies associated with DS (Dierssen, 2012). Brain structure is also altered in DS, with studies showing reduced cerebellar and cortical volume, and increased grey matter (Pearlson et al., 1998). An increase of cortical neurotransmitter Gamma Aminobutyric Acid (GABA) levels is associated with a greater density of grey matter versus white matter (Jensen, deB. Frederick, & Renshaw, 2005). Regulation of synaptic activity of neural cell assemblies of layer IV of the cortex is closely associated with parvalbumin (PV) interneuron activity (Northoff & Sibille, 2014). Alterations of the laminar architecture of grey matter in the cortex may result in abnormalities of GABA concentration. The role of cortical layer IV in

effective generation of thalamo-cortical looping implies potential impairments of GABAergic functioning, creating desynchronized temporal windows for neuronal firing and reducing gamma coherence (Fries, 2009). While global deficits of grey matter are observered in DS, white matter is reportedly preserved in the temporal lobes of the DS brain (Pinter, Eliez, Schmitt, Capone, & Reiss, 2001). An increase in cortical grey matter in DS may account for the reduction of phase coherence of the ASSR, suggesting DS individuals might have impaired inter-hemispheric communication. The dependence of effective cognitive functioning on gamma coherence (Fries, 2009), implies deficient integration in DS individuals.

2.2. Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive brain imaging modality recording the magnetic fields across the human head generated by electrical neuronal activity (Cohen, 1972). Unlike EEG, voltage difference between cortical locations,, the signal measured by MEG is not obstructed by the skull and scalp (Proudfoot, Woolrich, Nobre, & Turner, 2014). Recording of the magnetic field reflects neuronal oscillatory activity in near real-time (Brookes et al., 2011).

Despite the capability to provide the best non-invasive temporal resolution of brain activity, raw MEG data does not initially provide good spatial resolution. Harnessing the potential for spatially accurate brain mapping in MEG requires solving the “inverse problem” (Cheung, 2012), or finding the set of active sources in the cortex that can account for observed sensor measurements. This “inverse problem” of source localization presents a challenge in that it is mathematically ill-posed. An infinite number of solutions to the possible location of cortical activity sources can account for a given set of recordings at the sensor level. In response to the inverse problem, signal-processing techniques can be implemented. There are various methods of analysis that have been shown as robust and accurate measures of source localization. With these measures in place, MEG provides extremely sharp spatiotemporal resolution of cortical activity. Beamformers are a common example of a measure of source localization. This procedure applies a spatial filter to each source in the MEG, in order to supress sources of activity generated at other cortical locations (Quraan & Cheyne, 2010; Van Veen, Van Drongelen, Yuchtman, & Suzuki, 1997). This procedure yields a three-dimesnional representation of source activity in the brain.

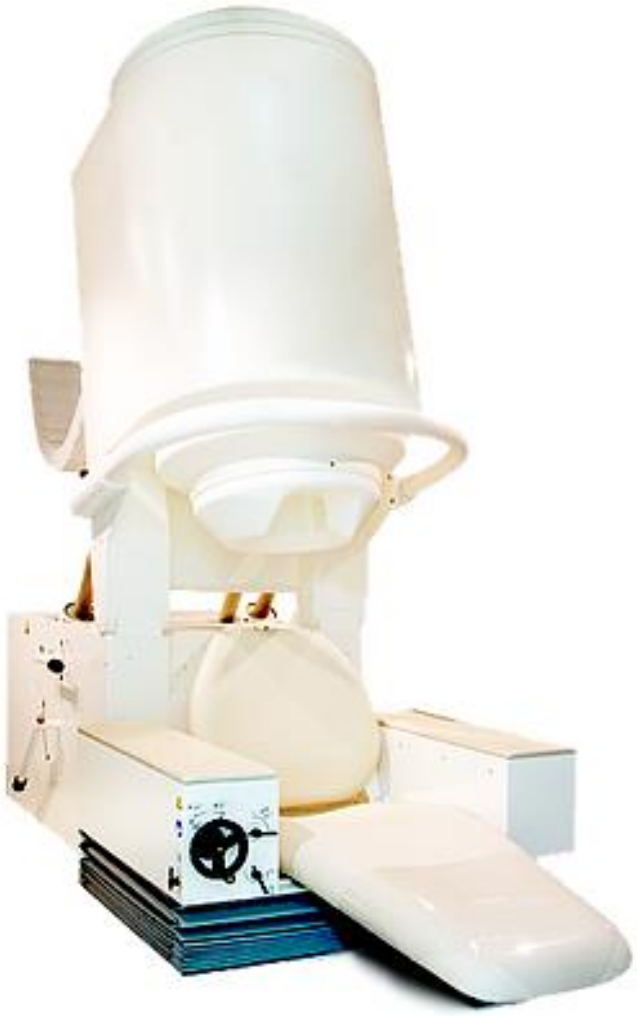

Figure 2.1. 151 Channel Full Head MEG Scanner identical to the MEG used for this study. Copyright 2017 by CTF MEG. Adapted with permission.

2.2.1. General Overview of Signal Analysis in MEG

A general understanding of MEG signals can be accomplished by addressing the underlying neurophysiological events associated with signal generation as well as the interpretation of signal analysis. Neuronal oscillations occurring on a sub-millisecond time scale can be detected with MEG, which primarily picks up the magnetic field of the excitatory post synaptic potential of pyramidal neurons (Cheung, 2012) . Current dipoles can be simply described as the summed activity of a cortical area, generated by the electrical current flowing through these cells (Hansen & Kringelbach, 2010). Dipole strength provides crucial information in the spatiotemporal analysis of MEG data.

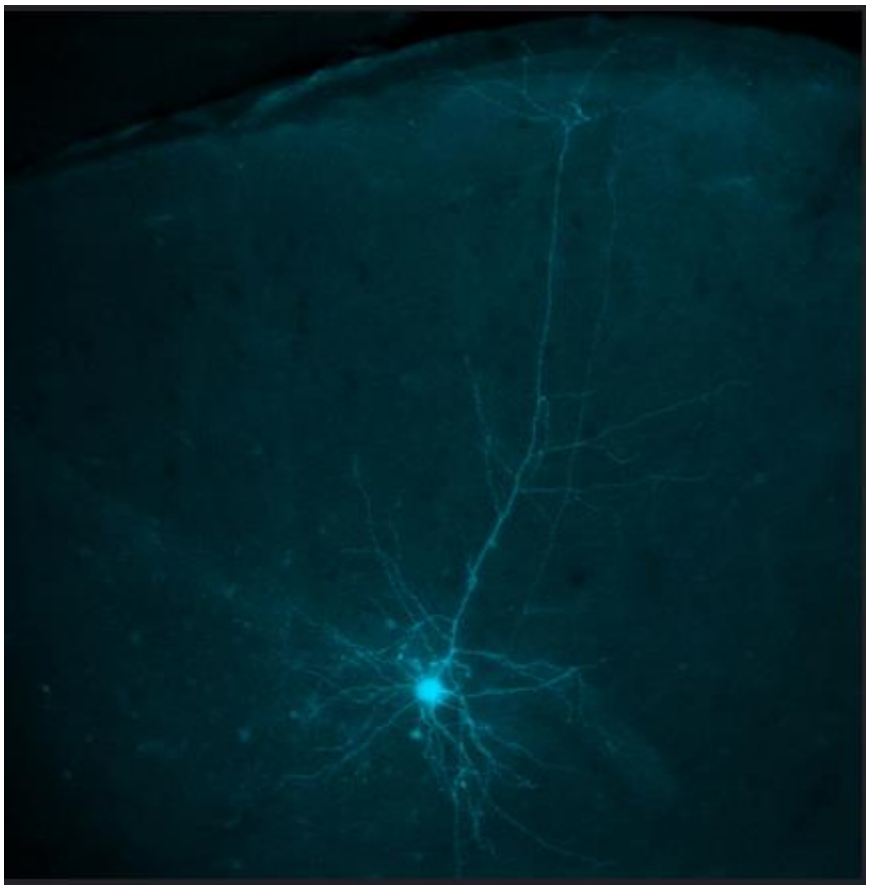

Figure 2.2. Pyramidal neuron. © Mark Miller, neurollero @ flickr

MEG signal generation can be classified as spontaneous or event-related (Pizzella et al., 2014). Event-related signals occur as a response to a stimulus or motor response, and can be further classified as evoked or induced responses. Evoked signals can be averaged across trials as they are phase and time locked. Induced signals are solely time locked, hence the signal is lost to noise during the signal averaging process. Event related signals in MEG show consistencies in phase or amplitude, known as Event Related Fields (ERFs). These ERFs can be used to study the brain's response to external stimuli in healthy and clinical populations (e.g. Tavabi, Obleser, Dobel, & Pantev, 2007).

2.3. Large Scale Integration

Electrical and chemical signalling across neurons is well understood to facilitate communication in the brain, but uncovering the precise mechanism by which the brain coordinates a unified perception of reality remains an ongoing pursuit. Cognitive

neuroscience continues to explore the neural processes which give rise to thoughts and emotions (Ward, 2003). Current knowledge integrates theory with empirical evidence of neural networks as seen with functional brain imaging modalities. A prevalent theory derived from M/EEG research suggests information integration in the brain is a result of neuronal coherence (Fries, 2015; Singer, 2010). This theory assumes neurons have the intrinsic ability to oscillate, and do so in such a way that creates rhythmic excitability patterns (Fries, 2005). These patterns create temporal opportunities to increase or decrease the likelihood of synaptic firing on a millisecond timescale (Whittington, Cunningham, Lebeau, Racca, & Traub, 2010). The rate of firing in these cell assemblies characterizes the frequency bandwidth, with gamma oscillations occurring in a 10-30 millisecond time window (Buszaki, 2012). These fast gamma oscillations are understood to subserve cortical computations as an underlying neural mechanism of functional connectivity in the brain (Kaiser & Lutzenberger, 2003). The combination of structural neural connectivity and neuronal coherence is thought to drive communication in the brain (Fries, 2009). Local integration refers to the communication of cells physically close to one another. In contrast, large-scale integration refers to groups of neurons connected through polysynaptic pathways across multiple regions of the brain (Varela et al., 2001). The interaction of integration processes via neuronal synchronization and neuroanatomical connections is widely speculated to play a crucial role in temporal binding, or the coordination of different areas of the brain to produce a unified perception of our environment.

2.4. Neural Path of Auditory Signals

The primary neural pathway of auditory signals starts at the cochlea, situated in the inner ear. Within the cochlea lies the organ of Corti, which is responsible for the transmission of signals to the auditory nerve. The basilar membrane at the base of the organ of Corti generates vibrations in response to sound. Hair cells within the organ of Corti vibrate at a particular frequency, creating electrical gradients that either excite or inhibit auditory nerve fibres that transfer information to the brain. The brainstem and thalamus receive the signal first, before the auditory cortex (Breedlove, Watson, & Rosenzweig, 2010). A thalamo-cortical loop is generated between the thalamus and auditory cortices; the disruption of which may lead to the impairment of auditory processing.

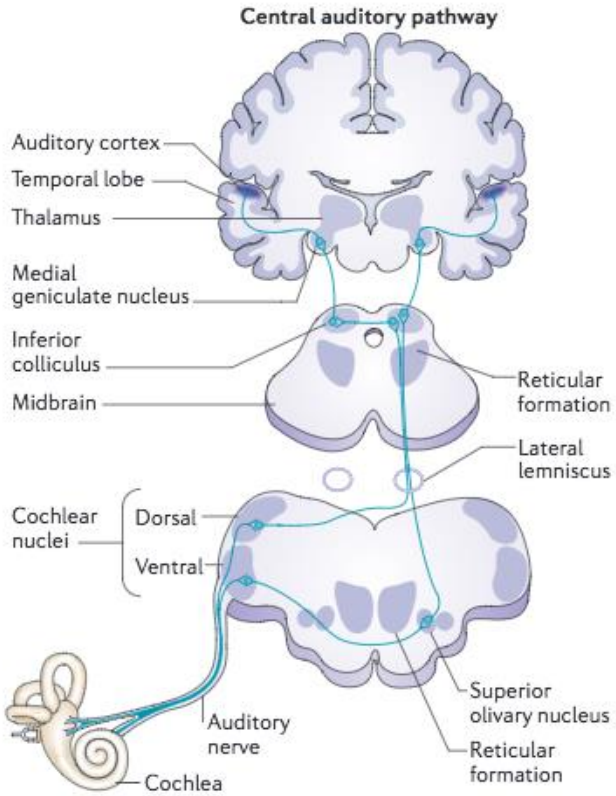

Figure 2.3. The human auditory pathway. Copyright 2015 by Javitt & Sweet. Adapted with permission.

2.5. The ASSR

The ASSR is a demonstrated and robust measure of neuronal activity.. Steady state responses result in consistent temporal phase and amplitude characteristics of oscillating neuronal rhythms. The ASSR is typically generated by a repetitive stimulus of clicks or amplitude modulated sine waves (Kuriki, Kobayashi, Kobayashi, Tanaka, & Uchikawa, 2013). The frequency at which the stimulus is administered drives neuronal oscillations of the same frequency in the auditory cortex (Mäkelä & Hari, 1987). A robust response, the ASSR shows a maximal amplitude at 40 Hz (Galambos et al., 1981). First labeled as the “40 Hz Event Related Potential (ERP)”, use of the ASSR has been cited in clinical settings as an assessment of hearing loss (Karawani, Attias, Shemesh, & Nageris, 2015; Pauli-Magnus et al., 2007). The ASSR is an especially beneficial tool due to the ability to evaluate physiological mechanisms without the need of a verbal response of the participant. In clinical populations such as DS, where the participant may

be cognitively low functioning, the ASSR may serve as a effective measure of neural circuit dysfunction.

The primary neural generator of the 40 Hz ASSR can be localized to the auditory cortex, with a component of activity in the midline brainstem (Plourde, Stapelles, & Picton, 1991). This brainstem activity is known as the Auditory Brainstem Response (ABR), and is also used as an assessment of hearing loss (McCreery et al., 2014). However, the ABR does not demonstrate sensitivity to tone frequencies that the perception of speech depends upon (Galambos et al., 1981).

The middle latency response (MLR) is an evoked potential occurring between 10-50 milliseconds after stimulus onset (Picton, 2010). It consists of a series of evoked waveforms, speculated by some as a contributor to the neural generator of the ASSR (Presacco, Bohórquez, Yavuz, & Özdamar, 2010).

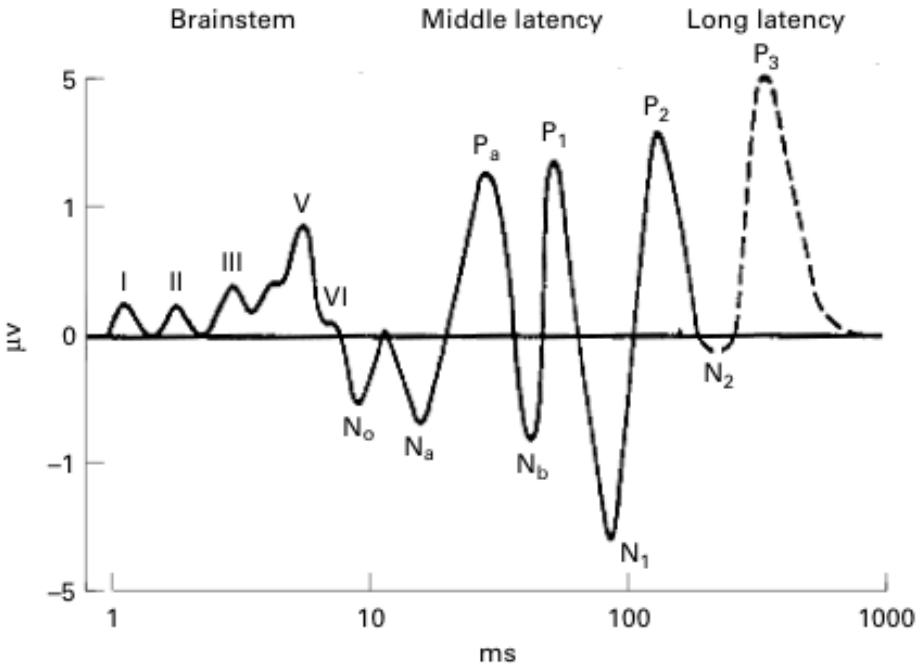

Figure 2.4. An auditory evoked potential. Copyright 1997 by Bailey and Jones. Reprinted with permission.

The precise mechanism of ASSR generation remains unknown. The literature presents a general disagreement as to the underlying neural mechanism of the ASSR. Two main theories currently exist in an effort to explain the origin of this response. The first theory considers the ASSR primarily an evoked response, as each click or tone

generates an auditory response (Azzena et al., 1995). The rapid presentation of oscillations in the gamma frequency band results in overlapping of MLR components, creating a peak in 40 Hz activity (Plourde et al., 1991). Deconvolution algorithms separate components of the 40 Hz rhythm and are reported as evidence of the linear addition of MLR peaks (Bohórquez & Özdamar, 2008; Gutschalk et al., 1999). The second theory explores the ASSR as a predominantly induced response, suggesting neurons with the intrinsic ability to oscillate do so with a maximal response at 40 Hz in a thalamo-cortical loop (Llinás, 2003). According to this model, rhythmic sensory input resets rhythmic activity in the network resulting in neuronal synchronization (Ross, Herdman, & Pantev, 2005). This theory suggests 40 Hz activity is a correlate of cognitive temporal binding (Joliot, Ribary, & Llinás, 1994). The mechanism of the ASSR was not specifically tested in this study, but the latter theory is implicated in the interpretation of the present results.

2.6. The Relationship between GABA and Gamma Oscillations

Cortical inhibitory neurotransmission by GABA is associated with the rate of neuronal firing (Chen et al., 2014). For typically developing individuals, GABA concentrations and gamma oscillations have been shown to be associated in visual (Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009), motor (Gaetz, Edgar, Wang, & Roberts, 2011) and auditory (Port, Gaetz, et al., 2016) regions of the brain. Abnormalities in GABA concentration in any given area of the cortex affects the rate of oscillatory activity, as perisomatic inhibitory activity of the PV interneurons modulates the temporal windows of excitation necessary for oscillatory activity (Buszaki, 2012). GABAergic signalling has been speculated to be atypical in DS based on extensive research revealing evidence of dysfunctional inhibitory neurotransmission in DS mouse models (For a review, see Contestabile, Magara, Cancedda, Tropea, & Cherubini, 2017).

2.6.1. ASSR in Schizophrenia

Other pathologies evidence a consistent deficiency in ASSR power or phase coherence, providing evidence for the ASSR as an appropriate evaluation of neural circuitry. Schizophrenia (SZ) is characterized by delusions, hallucinations and

disorganized speech (American Psychiatric Association, 2013). Investigation of the ASSR as a biomarker for SZ shows a strong association between 40 Hz phase locking and hypofunction of the excitatory neurotransmitter NMDA, indicating the ASSR could be a valuable tool in the evaluation of excitatory transmission (Sivarao et al., 2016). In vivo Magnetic Resonance Spectroscopy (MRS) research shows a relationship between gamma oscillations and GABAergic activity in SZ during a working memory task, implying a dependent relationship between gamma and GABA as is the case for normal brain function (Chen et al., 2014).

2.6.2. ASSR in Autism Spectrum Disorder

Atypical gamma oscillatory activity is reported in ASD (Cornew, Roberts, Blaskey, & Edgar, 2012; Ye et al., 2014). Investigation of ASSR in ASD has revealed a disruption of gamma activity, indicating a reduced capacity for information binding in the ASD brain (Wilson, Rojas, Reite, Teale, & Rogers, 2007). A well-established link between aberrant oscillations and GABA in ASD has contributed to the theory of an excitation-inhibition imbalance in the ASD brain (Rubenstein & Merzenich, 2003). Numerous studies have reported atypical GABA transmission in ASD (Cochran et al., 2015; Pizzarelli & Cherubini, 2011; Port, Gaetz, et al., 2016). As GABAergic interneurons demonstrate a close relationship to gamma band activity generation (Traub, Whittington, Colling, Buzsáki, & Jefferys, 1996), alterations of regular GABA transmission may play a key role in thalamo-cortical function and appropriate excitation and inhibition in neural circuits (Port, Edgar, et al., 2016) Speculation based on similar behavioural manifestations of symptoms of DS and ASD could suggest similarities of underlying neural pathologies of these conditions. Individuals with ASD are reported to experience abnormalities of gamma activity (Rojas & Wilson, 2014), including a reduction in phase locking of the N100m response in mouse models of ASD (Gandal et al., 2010).

2.7. Gamma Oscillations in Development

Neuronal synchronization plays an important role in the development of mature cortical networks. As the cerebral cortex develops, patterns of synchronization characterize functional networks that serve to create neural connections through the

precise timing of chemical neurotransmission (Gireesh & Plenz, 2008). Oscillatory activity is sensitive to GABAergic neurotransmission, specifically in the case of gamma band synchronization.

The relationship of excitatory and inhibitory transmission to specific cognitive developmental processes remains largely unknown. However, the presence of increased excitatory activity during cortical development is suggested to be related to improved neuroplasticity and the expansion of cognitive abilities (Cohen Kadosh, Krause, King, Near, & Cohen Kadosh, 2015). Neuroplasticity is understood to be largely mediated by GABAergic transmission (Lehmann, Steinecke, & Bolz, 2012). The implication of these findings may show relevance to the development of cortical networks in clinical populations that demonstrate cognitive impairments. Disruptions in the healthy development of the cortex can result in anatomical and physiological atypicalities that change patterns of neuronal oscillations (Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010), contributing to disorganized communication in the brain.

2.8. The Knowledge Gap

Individuals with DS reportedly demonstrate aberrant functional connectivity, but no existing neural marker of connectivity in the DS brain exists. A more robust understanding of oscillatory activity in the DS brain may prove useful in the treatment of DS symptoms. Studies show the symptoms of DS include impaired execution of higher cognitive processes (Byrne, MacDonald, & Buckley, 2002; Chapman & Hesketh, 2001), but the neural correlates of these symptoms have not been extensively explored. Inter-hemispheric phase locking during ASSR stimulation has yet to be studied in source space in the DS brain, and may provide some insight into the patterns of long-range neuronal oscillatory synchronization in the DS population. A deeper knowledge base of the oscillatory dynamics of the DS brain will build upon existing studies suggesting aberrant functional connectivity in DS, and may contribute to the development of more resources to treat the symptoms of DS.

Chapter 3. Objectives and Hypotheses

The goal of this thesis is to investigate the neural dynamics of the ASSR in DS. Oscillatory dynamics and their relationship to cognitive deficits in DS remains poorly understood. Using source space analysis in MEG, this thesis explores the inter-hemispheric phase and amplitude activity between the primary auditory cortices of DS and non-DS individuals. The probing of phase locking in response to the ASSR, using MEG and source space analysis, has not been examined to date to the best of our knowledge. This thesis also aims to make a substantial contribution of knowledge working toward the development of a neuronal oscillation-based model of the DS brain.

The hypotheses of this thesis are as follows:

1. Individuals with DS will exhibit less spectral power, when compared to controls, in response to the 40 Hz stimulus.

2. Individuals with DS will exhibit less inter-hemispheric phase locking in the auditory cortices when compared to controls.

Chapter 4. Methods

4.1. Data Collection

The data were collected between the years 2005 and 2009 at the Down Syndrome Research Foundation (DSRF) in Burnaby, B.C. Usage of these data for the present study is secondary, and participants have not been re-identified or contacted after data collection.

4.1.1. Participants

The present study was approved by the research ethics board of Simon Fraser University. Twelve individuals with Down Syndrome participated in the study, as well as twenty typical individuals in a control group. The mean age of the DS group was 12.7± 5.56 years, while the mean age of the control group was 15.3 ± 7.3 years. Control participants ranged from age 6-28, while DS particpants ranged in age from 5-26. There were sixteen females in the control group and six in the DS group, and groups were not statistically significantly different in terms of age (X^2,1,p = 0.26) or sex (X^2,1,p = 0.07). Exclusion criteria for these participants were the presence of any metal implants, hearing loss, or comorbid psychiatric or neurodevelopmental disorder. Hearing was assessed for each participant through the MEG sound delivery system at 500, 1000 and 4000 Hz using headphone inserts. Thresholds for hearing did not differ significantly between control and DS groups (Roberts et al., 2007). Every participant was briefed on study protocol, and provided written informed consent prior to the commencement of data collection. Individuals unable to provide consent gave their informed assent, with their legal guardians providing written informed consent for the participant to be involved in the study. All participants were provided with a small monetary compensation for their time.

4.1.2. Experimental Design

Participants were instructed to lie supine in the MEG, with MEG-compatible insert earphones in both ears for binaural stimulus presentation. A silent video was played to maintain eye position. A series of 40 Hz sinusoidal amplitude modulated tones (carrier

frequency 500+1000+4000 Hz) was presented to participants binaurally to evoke the ASSR. Twenty trains of 10-second continuous presentations of the stimulus were separated by intervals of silence lasting 500 milliseconds (Roberts et al., 2007).

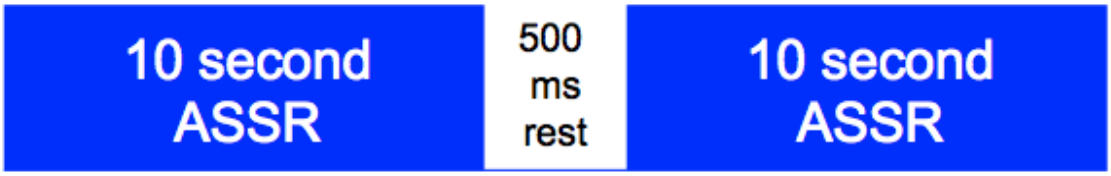

Figure 4.1. 10 seconds of ASSR were presented with 500 milliseconds of silence in between stimulus administration.

4.1.3. Data Acquisition Instruments

Data were acquired using a 151 channel full head MEG scanner (CTF Systems Inc., Port Coquitlam, Canada). Head shape was subsequently recorded using an Isotrak 3D Digitizer (Polhemus, Colchester, USA).

4.2. Data Analysis

4.2.1. Analysis Tools

MATLAB was the primary tool used for data analysis (MATLAB 2017a, The MathWorks, Inc.). FieldTrip, an open source toolbox for neuroimaging data analysis, , was implemented in MATLAB (Oostenveld, Fries, Maris, & Schoffelen, 2011). Raw data were initially visualized using DataEditor (CTF Systems Inc., Port Coquitlam, Canada) to observe potential bad channels, dipole strength, and 40 Hz activity. Visual examination of the data confirmed no bad channels. MRIViewer (CTF Systems Inc., Port Coquitam, Canada) was used to visualize individual polhemus points overlaid with a T1 weighted MRI image (*fig. 4.3*). Statistical analysis was partially completed using JMP®, Version *13* SAS Institute Inc., Cary, NC, 1989-2007.

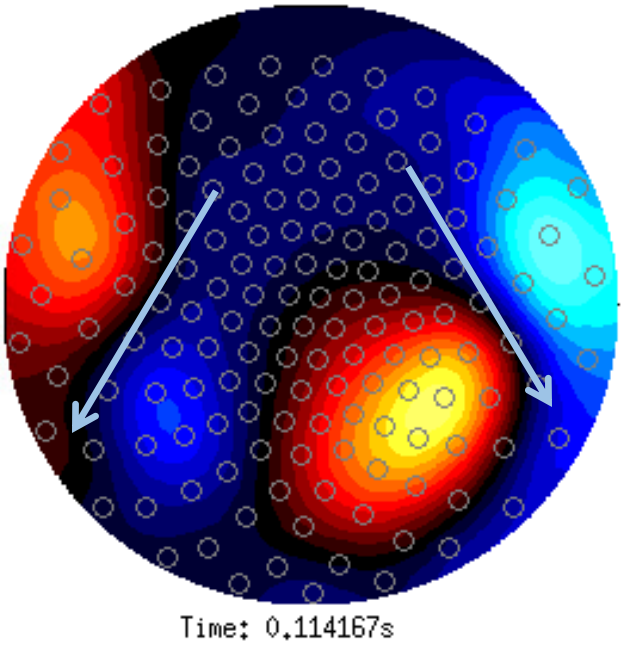

Figure 4.2. **Topography map of one control participant, indicating a bilateral dipole response at stimulus onset (114 milliseconds). Dipole currents are situated in between the negative red charge and positive blue charge. Arrows indicate direction of the current flow. Visualized using DataEditor.**

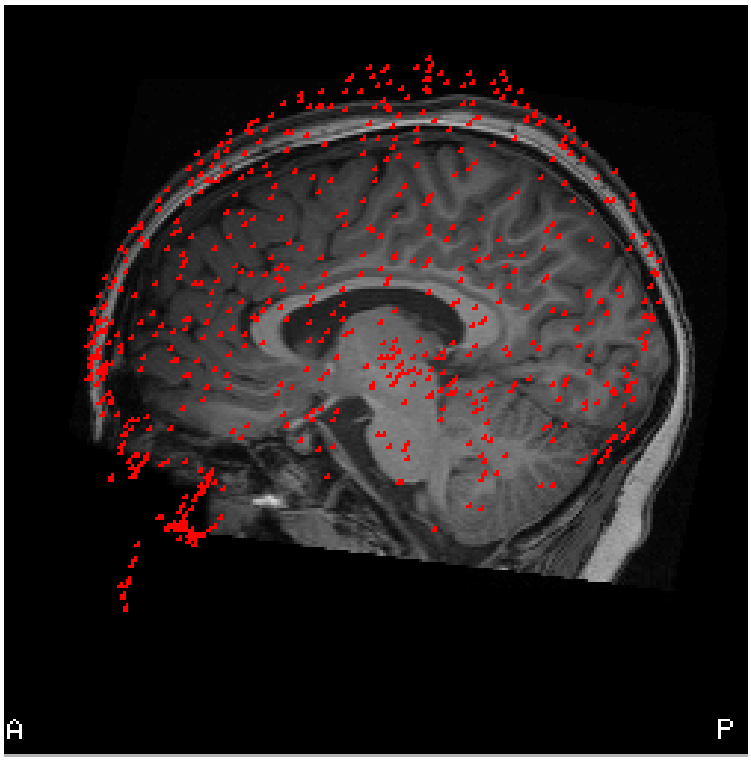

Figure 4.3. **Polhemus points (red) overlaid manually over a standard MRI in MRIViewer for visualization purposes.**

4.2.2. Analysis Procedure

Preprocessing

Raw data were initially redefined by implementing filters and segmenting trials to improve the signal to noise ratio. Data were then epoched, creating segments with a length of -0.5 to 5 seconds. A notch filter was applied at 60 and 120 Hz to account for line noise and harmonics. In addition, a bandpass filter (1-150 Hz) was used to remove low frequency drift generated by the signal and high frequency noise unrelated to brain activity. The sampling rate was decreased from 2400 Hz to 600 Hz. A third order spatial gradient noise cancellation was applied to reduce contamination of the signal from external sources of far field magnetic noise. Runs were concatenated into one set of trials per participant.

MRI Co-registration

A critical element of MEG analysis is the co-registration of data with a MRI image, as this process allows for source activity localization based on MEG data. Polhemus points were warped to a standard T1 weighted MRI image. Translation matrices are constructed in order to shift between coordinate systems necessary for effective co-registration. Data are recorded in a headspace coordinate system for the Polhemus digitizer, and then coordinates must be shifted to Montreal Neurological Institute (MNI) coordinate space, then to CTF MEG coordinate space to be consistent with the Polhemus and then back to MNI for the co-registration. Co-ordinates of fiducial points recorded at the time of data collection were manually placed on an MRI image over the left and right tragus, as well as the nasian point in MRIViewer.

Brain Parcellation and Beamforming

The brain was parcellated into 116 regions, based on the Automated Anatomic Labelling (AAL) Atlas. A 116 by 116 time series was constructed based on regions of interest representing cortical, sub-cortical and cerebellar regions. The AAL Atlas is effectively used in multimodal neuroimaging as a method parcellating the brain into regions of functional relevance (Tzourio-Mazoyer et al., 2002).

A beamformer is a spatial filter that allows for the detection of one signal originating at any given location while suppressing the strength of signals generated

from other cortical locations (Green & McDonald, 2009). This process is used to reconstruct source activity at a given region of the cortex. The Linearly Constrained Minimum Variance (LCMV) beamformer is more robust to sources of variability in the data, and is therefore an appealing option in the analysis of evoked signals (Van Veen et al., 1997). A three-dimensional construction of source power in the brain is created by separate beamformer procedures for each signal location. This process filters signals from separate locations throughout the brain, but is limited by the suppression of highly correlated sources. In order to extract seed points for analysis, an 8-millimeter grid was overlaid on the cortical surface. This grid contained 2914 points, and a separate beamformer procedure was run on each of these individual points representing the cortical surface. The 8-millimeter grid creates appropriate smoothing properties and each virtual sensor is treated as a separate source (Barnes, Hillebrand, Fawcett, & Singh, 2004). Grid points representing the left and right Heschl's gyrus were extracted and used for further analysis.

Individual sources situated in the Heschl's gyrus, based on the overlay of the beamformer grid on the parcellated brain were used for a time frequency analysis. The AAL atlas defines the right Heschl's gyrus with a volume of 1936 $mm^{3,}$ and the left with a volume of 1804 mm^3.Six points were utilized on the right auditory cortex and three points were utilized on the left auditory cortex. The difference can be accounted for due to anatomical differences between the left and right hemisphere, resulting in a larger size of the right Heschl's gyrus in the AAL atlas.

Spectral Power Analysis

A power spectrum was derived for both groups based on time locked data. All data were averaged across trials for each participant. Fourier transformations were done on the stacked time series data to obtain frequency and phase information. Canonical analysis of ASSR involves the investigation of spectral power to measure signal strength (Brenner et al., 2009). A common use of spectral power analysis is the potential capacity to measure spontaneous neural activity (Engel et al., 2013). Here, we use a spectral power analysis to examine strength of the stimulus between groups in the left and right primary auditory cortex.

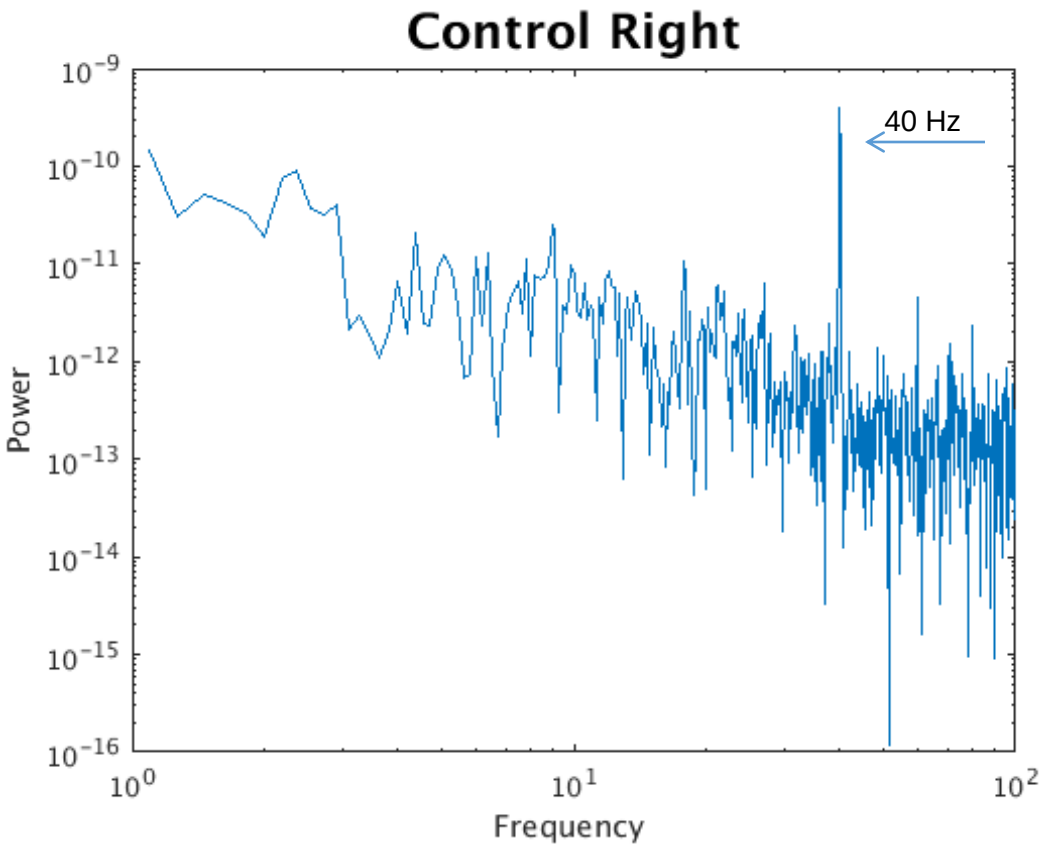

Figure 4.4. Spectral power of one control participant in the right hemisphere in response to the 40 Hz stimulus. Arrow points to peak 40 Hz activity.

Phase Locking Value

As a concept, synchronization can be described as changes in rhythmic patterns caused by the interaction of self-reliant oscillators (Ward & Doesburg, 2009). In order to measure an oscillation, it is necessary to break down a signal into two parts: its phase and its amplitude. Phase measures the point an oscillator is at within a given cycle. The amplitude is a measure of the magnitude, or height of an oscillation. As the concept relates to the brain, the phase of a neuronal oscillation is measured by extracting its position at any given time point.

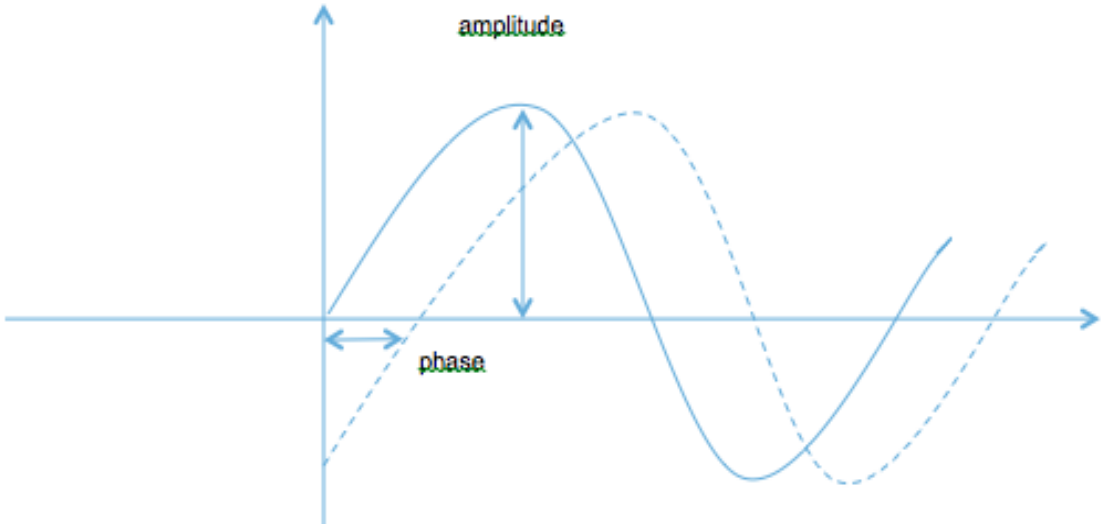

Figure 4.5. Phase difference and amplitude of a sine wave.

Assuming neuronal coherence is a mechanism for neuronal communication, phase locking value provides a valuable measure of oscillatory synchrony. Due to the problem of signal leakage in the collection of MEG data, accurate calculation of phase locking can be hindered by the introduction of spurious synchronization. Signal leakage in MEG refers to the inability to differentiate a linear mixing of signals originating from neighboring cortical sources (Gohel, Lee, Kim, Kim, & Jeong, 2017). Spurious synchronization results from uncorrelated oscillatory activity that appears to be occuring in synchrony (Zanin & Papo, 2013). As a result, some analysis methods remove zero-phase lag, or true synchronization; assuming these signals are actually noise (Hardmeier et al., 2014; Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011). This was not done in the present study, as the regions of interest are on opposite sides of the brain and are not likely to experience signal leakage.

A popular algorithm used in the analysis of phase coherence is Phase Locking Value (PLV), which retains the most phase information compared to other measures of phase coherence (Lachaux, Rodriguez, Martinerie, & Varela, 1999). This can pose an issue for the examination of neighboring cortical sources, due to the mixing of signals. However, the retention of phase information in the study of long-range connectivity is valuable. For this reason, PLV was chosen as the most appropriate measure for the present analysis. PLV is initially derived as a measure between – π and π to indicate the difference between the phase of two time sources, but is normalized through baseline

comparison to a value between 0 and 1, where 0 indicates no synchronization and 1 indicates perfect synchronization.

Here, we derived PLV using wavelet transformations, which decompose into frequency space. Wavelet transformations allow for the differentiation of phase information from the amplitude envelopes of neural signals generated in the left and right seed points associated with Heschl's gyrus at 40 Hz. Inter-hemispheric connectivity was assessed based on the averaged PLV between the left and right Heschl's gyrus. In order to test for differences between group PLV, a Mann-Whitney U test was used (Mann & Whitney, 1947). This statistical measure is useful in the comparison of groups that do not present a normal distribution.

Chapter 5. Results

5.1. Detection of 40 Hz ASSR and Spectral Power

Beamformer results successfully localized ASSR activity to the primary auditory cortex. This is consistent with existing literature (Herdman et al., 2003), and it is widely accepted that ASSR can be localized to the primary auditory cortex.

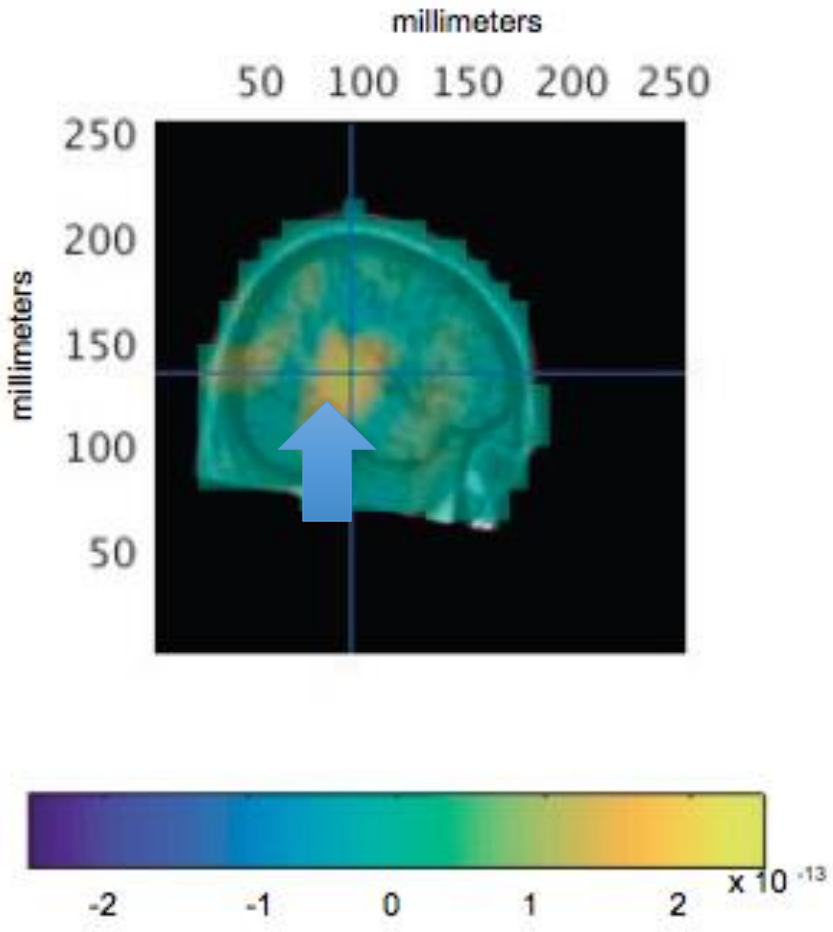

Figure 5.1. Sagittal view of one control participant showing activity localized to the right primary auditory cortex during ASSR stimulation.

Confirmation of the ASSR was observed by visual inspection of individual time frequency plots based on stacked trial data. Separate plots were generated representing the left and right Heschl's gyri.

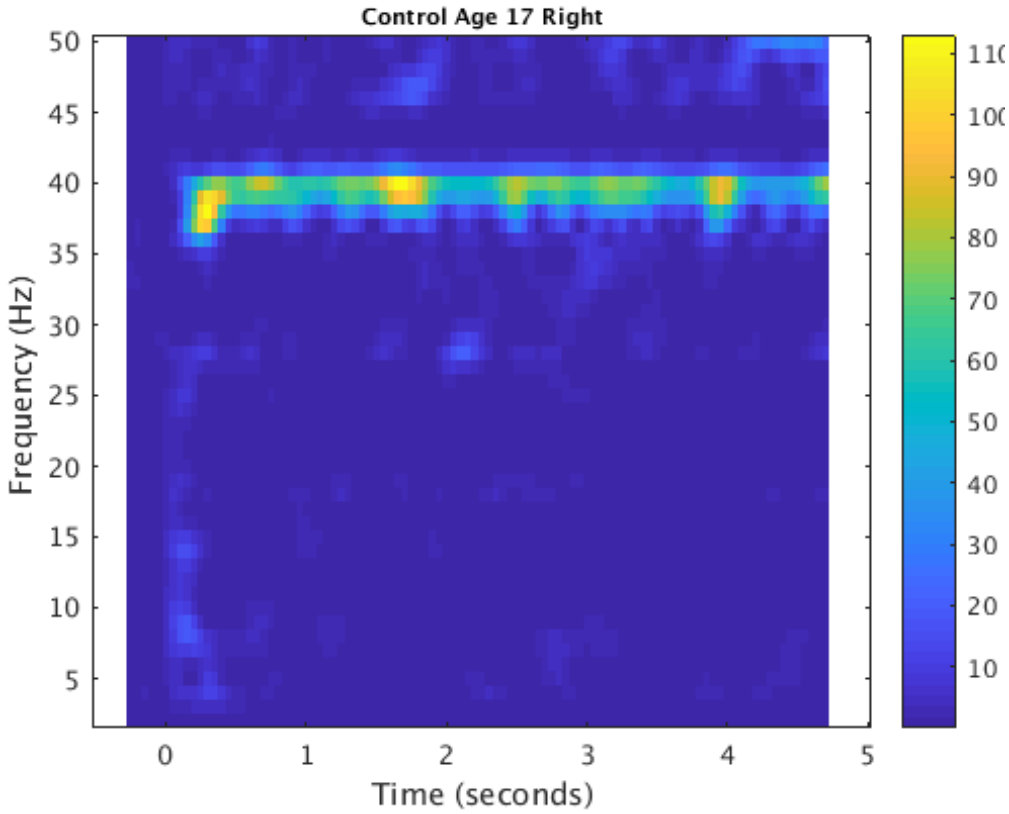

Figure 5.2. An example time frequency plot of one control participant in the right hemisphere. Plot indicates a strong gamma band activity at stimulus onset.

A beamformer procedure was implemented to describe surface signals in #D volumetric brain space. Source localization showed a large rightward bias. Separate from the weakness of the beamformer to differentiate highly correlated sources, magnetically recorded auditory signals often appear less powerful in the left hemisphere due to an increase in cortical folding (Shaw, Hämäläinen, & Gutschalk, 2013). A greater density of cortical matter results in a signal appearing diminished on the left.

The right side of the brain consistently showed a stronger 40 Hz signal across all participants (R^2 =0.85, 31, p< 0.0001). Between groups spectral power of the ASSR was also investigated. Visual inspection of spectral power confirms the hypothesized outcome of reduced spectral power in DS. However, a statistical significance of power between groups was not observed for either hemisphere (X^2, 29, p=0.32).

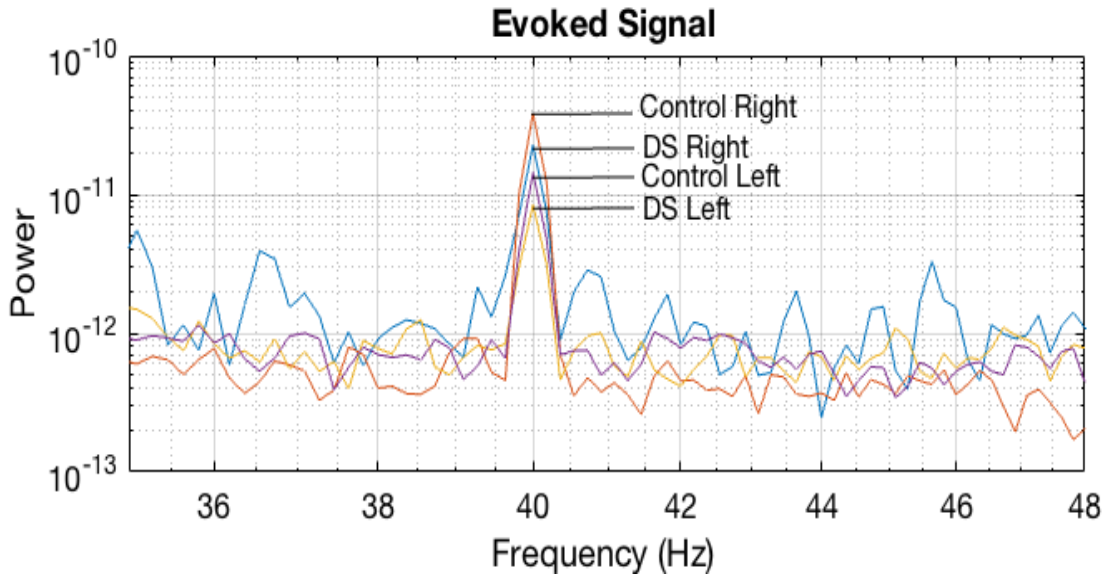

Figure 5.3. Averaged spectral power of each hemisphere for both control and DS groups. Visual inspection shows the highest peak in the right hemisphere of control participants and the lowest in the left hemisphere of DS participants.

5.2. Phase Locking Value

An investigation of inter-hemispheric phase locking between the left and right auditory cortex yielded a significant difference between groups (DS *U*= 187.0, C *U*= 53.0, $p < 0.01$). Individuals with DS show a significantly lower PLV based on the average stacked data. Between-groups comparison using a Mann-Whitney U test yielded a statistically significant effect between groups.

Chapter 6. Discussion

6.1. Integrative Processing in Down Syndrome

The results of this study provide evidence of reduced inter-hemispheric phase locking between left and right auditory cortex of DS individuals during ASSR stimulation. These results are consistent with the notion of disrupted gamma oscillatory activity in neurodevelopmental disorder (Rojas & Wilson, 2014), and complement behaviour-based findings of difficulties in higher cognitive processing experienced by DS individuals (Moore, Oates, Hobson, & Goodwin, 2002). Results suggest potential neuronal desynchronization in the gamma band and impaired GABAergic transmission and disruptions within thalamo-cortical loops. The probing of ASSR in DS yielded expected results in phase measures, but not in amplitude measures. Changes in both amplitude and phase of ASSR have been investigated, but ASSR has shown to be more robustly expressed as a phase change (Ross, 2008). A visually observed pattern can be detected in amplitude between groups *(fig. 5.3)* initially confirming our hypothesis of reduced spectral power in DS. However, the lack of statistical relevance would suggest the sample size may need to be increased in order to establish a reportable ASSR power effect in DS. The consistency of phase lag observed in ASSR, provides evidence of phase as a more appropriate measure to evaluate ASSR processing (Ross, 2008). In the present study the ASSR was robustly detected across groups but neuronal synchronization was impaired in the DS group. These findings suggest a neurological explanation of the cognitive deficits seen in DS, given the theory of neuronal coherence as a subserving mechanism of communication in the brain.

6.2. Gamma Oscillations and the Pathophysiology of Clinical Populations

The link between gamma oscillations and GABAergic transmission may indicate impairments in ASSR are relevant in the abnormal functioning of inhibitory neurotransmission (Lins & Picton, 1995; Vohs et al., 2010). Results indicate the reduced inter-hemispheric phase locking in DS could arise from an excitatory and inhibitory imbalance involved in information integration across neural cell assemblies. This notion

is consistent with abnormal transmission in DS mouse models (Kleschevnikov et al., 2004), and also aligns with the excitatory and inhibitory imbalance speculated as an underlying neural mechanism of ASD symptoms (Gogolla et al., 2009). Similarities in intellectual disabilities observered in both ASD and DS populations may be a result of similar underlying neural mechanisms, given the relationship of gamma oscillatory activity and GABAergic transmission in the function of thalamo-cortical looping (Joliot et al., 1994).

DS individuals have a high risk of developing AD at a younger age than a neurotypical person (Powell et al., 2014). In a post-mortem study of one hundred DS brains examined for similarity to AD, findings indicated DS individuals were three times more likely to show signs of AD than in the neurotypical population (Wisniewski, Wisniewski, & Wen, 1985). Past studies show atypical processing of 40 Hz auditory stimuli (Ribary et al., 1991) and ASSR (Osipova et al., 2006) in AD. Our findings confirm DS and AD respond similarly to the ASSR, indicating a potential relationship of gamma processing between the two conditions.

Reduced spectral power and phase infomation in response to ASSR stimulation is seen in SZ (Kwon et al., 1999). Speculation of the relationship of ASSR to effective neural circuitry, as modulated by GABAergic transmission, suggests that ASSR abnormality could be a biomarker for SZ (O'Donnell et al., 2013). Reports of atypicalities in ASSR and overall gamma processing in clinical populations supports the use of ASSR as a measure of gamma integration. The robust nature of the response, and the consistency of ASSR deficit in clinical populations may indicate a similar causal neural mechanism. Similarities in neurodevelopmental issues found in both ASD and DS may be comparable in the context of disrupted neural circuitry manifesting as particular behavioural symptomology.

The full extent of genetic influence on the manifestation of DS symptoms is not understood. Evidence suggests an imbalance of individual genes affects expression of chromosome 21, resulting in phenotypical anomalies associated with DS (Dierssen, 2012). Brain structure is also altered in DS, with studies showing reduced cerebellar and cortical volume, and increased grey matter (Pearlson et al., 1998). An increase of cortical GABA levels is associated with a greater density of grey matter versus white matter (Jensen et al., 2005), implying potential impairments of GABAergic functioning.

These impairments generate desynchronized temporal windows for neuronal firing and reducing gamma coherence. An increase in cortical grey matter in DS may account for the reduction of phase coherence of the ASSR, suggesting DS individuals display atypical inter-hemispheric communication. The dependence of effective cognitive functioning on gamma coherence (Fries, 2009), implies deficient integration in DS individuals.

6.3. Limitations of this Research

6.3.1. The Inverse Problem

The inverse problem presented in M/EEG data analysis does not yield a precise representation of source activity in the brain, due to the inability to distinguish signals detected from two different sensor locations (Wens et al., 2015). In the case of volume conduction in the brain, the potential inaccuracies of source activity localization causes an inevitable confounding factor in the collection of M/EEG data. Signal leakage is another challenge presented in the recording of M/EEG data. It introduces spurious activity into the data analysis, causing a primary confound in the effective interpretation of data (Palva and Palva, 2012). This problem is compounded by the presence of spurious activity caused by internal rhythms of the body separate from the brain, and external environmental noise picked up by the sensors (Gross et al., 2013). The ill-posed nature of the inverse problem of source localization in M/EEG necessarily creates a degree of spatial ambiguity, and spurious synchronization can never be completely omitted from data collection. For this reason, our results should be interpreted with a degree of caution.

6.3.2. MRI Co-registration

MRI co-registration is most effective with the acquisition of the personal MRI image of the individual, for the reason that a precise match to MEG data can be made. Due to the DSRF being equipped with only a MEG, MRI images for each participant were unavailable. Past research has challenged this difficulty with either utilizing a best-fit MRI match from an existing database (e.g. Virji-Babul et al., 2010) or to warp a standard MRI to the polhemus points of each individual (Mattout, Henson, & Friston, 2007). Due to the unavailability of a MRI database of DS individuals, this project took

advantage of the latter method. Despite anatomical differences in individual brains, this method has been deemed an effective way to co-register an MRI image to MEG data. However, the potential for anatomical differences between groups may slightly alter localization of points over an MRI image.

The possibility of slight imprecisions in MRI co-registration may be greater in this data due to the measurement of head localization coils before and after the scan, as opposed to the current method of continuous head localization. While head movement was accounted for, the lack of continuous head localization creates the possibility the participant's head moved in the dewar during the scan. Greater head movement could create inaccuracies in the fitting of fiducial points to the MRI image. While MRI co-registration can generally be achieved using a standard MRI and approximate fiducial locations, this is less desirable as it may be less precise.

6.3.3. Signal to Noise

The overlay of the beamformer grid with the AAL atlas generated six and three virtual channels on the right and left Heschl's gyrus, respectively. This asymmetry causes a discrepancy in the signal to noise ratio between hemispheres, and may be a counfounding factor in the interpretation of the spectral power analysis. While we would expect a rightward bias in MEG ASSR signal due to anatomical asymmetry (Shaw et al., 2013), the disproportionate number of points chosen due to the nature of the analysis causes difficulty in understanding whether the bias is due to neuroanatomy or analysis methodology.

6.3.4. Sample Size

Results of the spectral power analysis suggest the expected trend of amplitude during ASSR stimulation, with control participants showing the highest amplitude and DS patients showing a lower amplitude response at 40 Hz. However, upon statistical analysis this observed trend was not significant. Due to individual differences in the amplitude of the response to ASSR stimulation, statistically significant differences may

be observed only with a larger sample size. For this reason, the sample size in the present project is considered a limitation of this study.

6.3.5. Comorbid Disorders with Down Syndrome

Even though this study took into account participants with no other psychiatric or neurodevelopmental conditions, it is common to have people with DS show other signs of neuropsychological disturbances. For example, individuals with DS often present a diagnosis of ASD as well (Kent, Evans, Paul, & Sharp, 2007). Given some commonality in the manifestion of behavioural symptoms of both disorders and the limited knowledge of the neural consequences of ASD and DS, a discrepancy between the underlying causes of symptomology may not be made. Here, we do not test individuals with any other psychiatric or neurodevelpmental disorder other than DS so a generalization of these findings to the DS population cannot be made.

6.3.6. ASSR as a Primarily Induced Response

There is an absence of conclusive evidence in the literature to suggest a mechanism by which the disruption of ASSR occurs in DS therefore, a definite interpretation of these results cannot be made.The present interpretation of these results suggest impairment of intrinsic oscillatory activity within a thalamo-cortical loop at 40 Hz. This would suggest the ASSR is primarily an induced response, generated by natural resonance and phase reset of the 40 Hz oscillation (Ross & Fujioka, 2016). The dependence of 40 Hz oscillations in layer IV of the cortex depends upon the feed-forward inhibitory activity of GABAergic interneurons (Llinás, 2003). This feed forward activity implies dependence on an evoked response as well as a natural induced reponse in the ASSR, in order for the thalamo-cortical loop to function effectively. If the 40 Hz oscillation is indeed primarily composed of the stacking of the MLR (Galambos et al., 1981), the evoked response generated may rely on feed-forward mechanisms independent of intrinsic oscillations. This theory suggests the ASSR as a primarily evoked response with critical dependence on the timing of signal processing. With the disruption of the precise temporal windows needed for gamma coherence, both theories of ASSR generation depend on effective feed forward mechanisms.

6.4. Future Directions

6.4.1. Implications of ASSR and MEG Imaging

Further research might investigate multiple frequency bands of activity in response to the ASSR. Despite the canonical response of the stimulus driving a response in the gamma band, the role of cross frequency coupling (CFC) is becoming evident in the investigation of neuronal communication (Tort, Komorowski, Eichenbaum, & Kopell, 2010). CFC is speculated as part of the mechanism of large-scale integration in the brain, through the coupling of high and low frequency neuronal oscillations (Canolty & Knight, 2010). Future potential of CFC in MEG research may investigate the network dynamics of neuronal oscillations in response to the ASSR. The utilization of phase-amplitude interactions of CFC in MEG is a relatively new methodological approach to study long-range network dynamics as previously detected with fMRI, but with the spatiotemproal acuity of MEG (Florin & Baillet, 2015). The interaction of frequency bandwidths may provide an interesting avenue to pursue, given the mounting evidence suggesting the modulation of cross frequency interactions in the integration of neural information .

6.4.2. Psychometric Testing

Individuals with DS have varying levels of intellectual difficulty, but the experimental design of this project did not involve any psychometric testing which could yield further information regarding the functioning level of each participant. Potential differences in functional connectivity may exist between individuals with varying levels of cognitive abilities that may not be reflected in the present study. Variations in connectivity have been observered in ASD groups, based on symptom severity (Kwon et al., 1999). The subdivision of heterogenous groups within the DS population may yield idiosyncratic patterns of connectivity based on level of cognitive impairment. Future studies may explore functional connectivity using a robust measure such as ASSR, in combination with psychometric testing, to establish any idiosyncrasies present in level of functioning in the DS population. A valuable investigation might explore the range of functional domains related by the ASSR in DS, in order to establish the validity of using the ASSR as a global measure of information integration in the brain. Information

presented with psychometric testing may provide enough information to identify functional connectivity patterns in DS.

6.4.3. ASSR in Clinical Settings

The ASSR has demonstrated potential as a biomarker for conditions such as ASD or SZ; the diagnoses of both conditions is based on behavioural obervations of symptom manifestation (American Psychological Association, 2013). DS is characterized by an extra chromosome 21, so a need for a brain-based biomarker of the condition is redundant. However, a robust measure of neuronal activity in DS may be useful. Behavioural treatments of DS have proven to be extremely?? effective, but a primary drawback of these measures is the reliance on evaluator judgement, which is subjective, vulnerable to bias, and can vary on a case-by-case basis. The use of a robust response such as the ASSR can be effectively used to monitor treatment efficacy as a complement to regular behaviour-based treatment measures. In especially low functioning individuals, the ASSR may prove to be an applicable method of testing treatment progress as these individuals may not be able to verbally communicate effectively. Early symptom treatment for these individuals may improve overall functioning. Monitoring theraputic interventions for these individuals with the ASSR may provide an understanding of whether treatment is effective, provided a robust pattern of ASSR can be observed in the DS brain.

Chapter 7. Conclusion

By examining the ASSR, we are able to speculate about the neural mechanisms of symptoms creating difficulties in DS cognition. The results of this study provide evidence of deficient long range communication in the DS brain, in specific regards to reduced inter-hemispheric phase locking during ASSR stimulation. The repetitive 40 Hz stimulation drives intrinsic oscillatory activity in the primary auditory cortex of humans and is implicated in the effective integration of information in the brain. GABAergic transmission contributes to the modulation of precisely timed temporal windows, resulting in the rhythmogenesis of the gamma frequency band. Disrupted gamma synchronization is relevant to an imbalance of excitatory and inhibitory neurotransmission, affecting the successful execution of higher cogitive processes in special populations.

The purpose of this study is the specific investigation of large-scale integration in the DS brain using the ASSR. Results demonstrate a significant decrease in phase locking for DS participants compared to controls, indicating interrupted thalamo-cortical circuitry. Previous findings of aberrations of functional connectivity in DS are consistent with the results of this study. Next steps in research may explore the cross frequency relationship of the ASSR in DS, as well as examine a model of connectivity based on the whole brain. These findings complement behavioural measures of DS functioning, and may be useful in a clinical practice as a measure of treatment efficacy.

The results of this study indicate the phase and amplitude properties of the ASSR may be an appropriate measure of functional connectivity in the gamma band. Relevance of phase coherence of gamma oscillations for integration is observed in the normal brain, and reflects effective functioning and execution of higher cognitive processes. In addition to the existing clinical application of the ASSR as a measure of hearing thresholds, using the ASSR in source space MEG studies may prove extremely useful in the measure of neural circuitry in typical and atypical brains.

References

Anderson, J. S., Nielsen, J. A., Ferguson, M. A., Burback, M. C., Cox, E. T., Dai, L., … Korenberg, J. R. (2013). Abnormal brain synchrony in Down Syndrome. *NeuroImage: Clinical*, *2*(1), 703–715. https://doi.org/10.1016/j.nicl.2013.05.006

Annus, T., Wilson, L. R., Acosta-Cabronero, J., Cardenas-Blanco, A., Hong, Y. T., Fryer, T. D., … Nestor, P. J. (2017). The Down syndrome brain in the presence and absence of fibrillar β–amyloidosis. *Neurobiology of Aging*, *53*, 11–19. https://doi.org/10.1016/j.neurobiolaging.2017.01.009

Aydore, S., Pantazis, D., & Leahy, R. M. (2013). A note on the phase locking value and its properties. *NeuroImage*, *74*, 231–244. https://doi.org/10.1016/j.neuroimage.2013.02.008

Azzena, G. B., Conti, G., Santarelli, R., Ottaviani, F., Paludetti, G., & Maurizi, M. (1995). Generation of human auditory steadystate responses (SSRs). I: Stimulus rate effects. *Hearing Research*, *83*(1–2), 1–8. https://doi.org/10.1016/0378-5955(94)00184-R

Babiloni, C., Albertini, G., Onorati, P., Muratori, C., Buffo, P., Condoluci, C., … Rossini, P. M. (2010). Cortical sources of EEG rhythms are abnormal in down syndrome. *Clinical Neurophysiology*, *121*(8), 1205–1212. https://doi.org/10.1016/j.clinph.2010.02.155

Bailey, A. R. and Jones, J. G. (1997), Patients' memories of events during general anaesthesia. Anaesthesia, 52: 460–476. doi:10.1111/j.1365-2044.1997.133-az0134.x

Balarajan, R., Donnan P, S., & Adelstein M, A. (1982). Mortality and cause of death in Down's syndrome. *Journal of Epidemiology & Community Health*, *36*(2), 127–129. https://doi.org/10.1136/jech.36.2.127

Barnes, G. R., Hillebrand, A., Fawcett, I. P., & Singh, K. D. (n.d.). Realistic Spatial Sampling for MEG Beamformer Images. https://doi.org/10.1002/hbm.20047

Bittles, A. H., Bower, C., Hussain, R., & Glasson, E. J. (2007). The four ages of Down syndrome. *The European Journal of Public Health*, *17*(2), 221–225. https://doi.org/10.1093/eurpub/ckl103

Bohórquez, J., & Özdamar, Ö. (2008). Generation of the 40-Hz auditory steady-state response (ASSR) explained using convolution. *Clinical Neurophysiology*, *119*(11), 2598–2607. https://doi.org/10.1016/j.clinph.2008.08.002

Breedlove, M. S., Watson, N. V., & Rosenzweig, M. R. (2010). Hearing, Vestibular Perception, Taste and Smell. In *Biological Psychology* (6th ed., pp. 247–260). Sinauer Associates, Inc.

Brenner, C. A., Krishnan, G. P., Vohs, J. L., Ahn, W.-Y., Hetrick, W. P., Morzorati, S. L., & O'Donnell, B. F. (2009). Steady state responses: electrophysiological assessment of sensory function in schizophrenia. *Schizophrenia Bulletin*, *35*(6), 1065–77. https://doi.org/10.1093/schbul/sbp091

Brookes, M. J., Hale, J. R., Zumer, J. M., Stevenson, C. M., Francis, S. T., Barnes, G. R., … Nagarajan, S. S. (2011). Measuring functional connectivity using MEG: methodology and comparison with fcMRI. *NeuroImage*, *56*(3), 1082–104. https://doi.org/10.1016/j.neuroimage.2011.02.054

Buszaki G., W. X. J. (2012). Mechanisms of gamma oscillations. *Annu Rev Neurosci.*, *35*, 203–225. https://doi.org/10.1146/annurev-neuro-062111-150444.Mechanisms

Byrne, A., MacDonald, J., & Buckley, S. (2002). Reading, language and memory skills: A comparative longitudinal study of children with Down syndrome and their mainstream peers. *British Journal of Educational Psychology*, *72*(4), 513–529. https://doi.org/10.1348/00070990260377497

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*(11), 506–15. https://doi.org/10.1016/j.tics.2010.09.001

Chapman, R., & Hesketh, L. (2001). Language, cognition, and short-term memory in individuals with Down syndrome. *Down Syndrome Research and Practice*, *7*(1), 1–7. https://doi.org/10.3104/reviews.108

Chen, C.-M. A., Stanford, A. D., Mao, X., Abi-Dargham, A., Shungu, D. C., Lisanby, S. H., … Kegeles, L. S. (2014). GABA level, gamma oscillation, and working memory performance in schizophrenia. *Elsevier*, *4*, 531–539. https://doi.org/10.1016/j.nicl.2014.03.007

Cheung, T., & Cheung, T. (2012). APPLICATIONS AND ANALYSIS STRATEGIES OF MAGNETOENCEPHALOGRAPHY IMAGING by.

Cochran, D. M., Sikoglu, E. M., Hodge, S. M., Edden, R. A. E., Foley, A., Kennedy, D. N., … Frazier, J. A. (2015). Relationship among Glutamine, γ-Aminobutyric Acid, and Social Cognition in Autism Spectrum Disorders. *Journal of Child and Adolescent Psychopharmacology*, *25*(4), 314–22. https://doi.org/10.1089/cap.2014.0112

Cohen Kadosh, K., Krause, B., King, A. J., Near, J., & Cohen Kadosh, R. (2015). Linking GABA and glutamate levels to cognitive skill acquisition during development. *Human Brain Mapping*, *36*(11), 4334–4345. https://doi.org/10.1002/hbm.22921

Contestabile, A., Magara, S., Cancedda, L., Tropea, D., & Cherubini, E. (2017). The GABAergic Hypothesis for Cognitive Disabilities in Down Syndrome. *Front. Cell. Neurosci*, *11*. https://doi.org/10.3389/fncel.2017.00054

Cornew, L., Roberts, T. P. L., Blaskey, L., & Edgar, J. C. (n.d.). Resting-State Oscillatory Activity in Autism Spectrum Disorders. https://doi.org/10.1007/s10803-011-1431-6

David Cohen. (1972). Magnetoencephalography: Detection of the Brain's Electrical Activity with a Superconducting Magnetometer on JSTOR. *Science*, *175*(4022), 664–666.

Derbent, M., & Tokel, K. (2004). Congenital Heart Defects in Patients With Down Syndrome. In J. A. Mallard (Ed.), *Focus on Down Syndrome Reseach* (pp. 83–86). Hauppauge: Nova Science Publishers, Inc.

Dierssen, M. (2012). Down syndrome: the brain in trisomic mode. *Nature Reviews Neuroscience*, *13*(12), 844–858. https://doi.org/10.1038/nrn3314

Doesburg, S. M., & Ward, L. M. (2009). Synchronization analysis in EEG and MEG. In T. C. Handy (Ed.), *Brain Signal Analysis: Advances in neuroelectric and neuromagnetic methods*.

Ellis, H. (2013). John Langdon Down: Down's syndrome. *Journal of Perioperative Practice*, *23*(12), 296–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24404709

Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Sciences*, *5*(1), 16–25. https://doi.org/10.1016/S1364-6613(00)01568-0

Florin, E., & Baillet, S. (2015). The brain's resting-state activity is shaped by synchronized cross-frequency coupling of neural oscillations. *NeuroImage*, *111*, 26–35. https://doi.org/10.1016/j.neuroimage.2015.01.054

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2005.08.011

Fries, P. (2009). Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. *Annual Review of Neuroscience*, *32*(1), 209–224. https://doi.org/10.1146/annurev.neuro.051508.135603

Fries, P. (2015). Rhythms for Cognition: Communication through Coherence. *Neuron*, *88*(1), 220–235. https://doi.org/10.1016/j.neuron.2015.09.034

Gaetz, W., Edgar, J. C., Wang, D. J., & Roberts, T. P. L. (2011). Relating MEG measured motor cortical oscillations to resting ??-Aminobutyric acid (GABA) concentration. *NeuroImage*, *55*(2), 616–621. https://doi.org/10.1016/j.neuroimage.2010.12.077

Galambos, R., Makeig, S., & Talmachoff, P. J. (1981). A 40-Hz auditory potential recorded from the human scalp. *Proceedings of the National Academy of Sciences of the United States of America*, *78*(4), 2643–7.

Gandal, M. J., Edgar, J. C., Ehrlichman, R. S., Mehta, M., Roberts, T. P. L., & Siegel, S. J. (2010). Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biological Psychiatry*, *68*(12), 1100–6. https://doi.org/10.1016/j.biopsych.2010.09.031

Gireesh, E. D., & Plenz, D. (2008). Neuronal avalanches organize as nested theta- and beta/gamma-oscillations during development of cortical layer 2/3. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(21), 7576–81. https://doi.org/10.1073/pnas.0800537105

Gogolla, N., Leblanc, J. J., Quast, K. B., Südhof, T. C., Fagiolini, M., & Hensch, T. K. (n.d.). Common circuit defect of excitatory-inhibitory balance in mouse models of autism. Retrieved from https://jneurodevdisorders.biomedcentral.com/track/pdf/10.1007/s11689-009-9023-x?site=jneurodevdisorders.biomedcentral.com

Gohel, B., Lee, P., Kim, M.-Y., Kim, K., & Jeong, Y. (2017). MEG Based Functional Connectivity: Application of ICA to Alleviate Signal Leakage. *IRBM*, *38*(3), 127–137. https://doi.org/10.1016/j.irbm.2017.03.002

Green, J. J., & McDonald, J. J. (2009). A practical guide to beamformer source recontruction for EEG. In T. C. Handy (Ed.), *Brain Signal Analysis: Advances in neuroelectric and neuromagnetic methods* (pp. 79–99). Boston.

Gutschalk, A., Mase, R., Roth, R., Ille, N., Rupp, A., Hähnel, S., … Scherg, M. (1999). Deconvolution of 40 Hz steady-state fields reveals two overlapping source activities of the human auditory cortex. *Clinical Neurophysiology*, *110*(5), 856–868. https://doi.org/10.1016/S1388-2457(99)00019-X

Hansen, P., & Kringelbach, M. (2010). *MEG: An Introduction to Methods*. Oxford Scholarship Online .

Hardmeier, M., Hatz, F., Bousleiman, H., Schindler, C., Stam, C. J., & Fuhr, P. (2014). Reproducibility of Functional Connectivity and Graph Measures Based on the Phase Lag Index (PLI) and Weighted Phase Lag Index (wPLI) Derived from High Resolution EEG. *PLoS ONE*, *9*(10), e108648. https://doi.org/10.1371/journal.pone.0108648

Herdman, A. T., Wollbrink, A., Chau, W., Ishii, R., Ross, B., & Pantev, C. (n.d.). Determination of activation areas in the human auditory cortex by means of synthetic aperture magnetometry. https://doi.org/10.1016/S1053-8119(03)00403-8

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (n.d.). Electrical Signs of Selective Attention in the Human Brain. *Source: Science, New Series*, (22), 177–18036.

Isomura, S., Onitsuka, T., Tsuchimoto, R., Nakamura, I., Hirano, S., Oda, Y., … Kanba, S. (2016). Differentiation between major depressive disorder and bipolar disorder by auditory steady-state responses. *Journal of Affective Disorders*, *190*, 800–806. https://doi.org/10.1016/j.jad.2015.11.034

Javitt, D. C., & Sweet, R. A. (2015). Auditory dysfunction in schizophrenia: Integrating clinical and basic features. *Nature Reviews: Neuroscience*, *16*(9), 535–550. https://doi.org/10.1038/nrn4002

Jensen, J. E., deB. Frederick, B., & Renshaw, P. F. (2005). Grey and white matter GABA level differences in the human brain using two-dimensional,J-resolved spectroscopic imaging. *NMR in Biomedicine*, *18*(8), 570–576. https://doi.org/10.1002/nbm.994

Joliot, M., Ribary, U., & Llinás, R. (1994). Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(November), 11748–11751. https://doi.org/10.1073/pnas.91.24.11748

Kaiser, J., & Lutzenberger, W. (2003). Induced gamma-band activity and human brain function. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *9*(6), 475–484. https://doi.org/10.1177/1073858403259137

Karawani, H., Attias, J., Shemesh, R., & Nageris, B. (2015). Evaluation of noise-induced hearing loss by auditory steady-state and auditory brainstem-evoked responses. *Clinical Otolaryngology*, *40*(6), 672–681. https://doi.org/10.1111/coa.12448

Kent, L., Evans, J., Paul, M., & Sharp, M. (2007). Comorbidity of autistic spectrum disorders in children with Down syndrome. *Developmental Medicine & Child Neurology*, *41*(3), 153–158. https://doi.org/10.1111/j.1469-8749.1999.tb00574.x

Kidd, L. (1992). Cardiorespiratory Problems in Children with Down Syndrome. In I. Lott & E. E. McCoy (Eds.), *Down Syndrome Advances in Medical Care* (pp. 61–69). New York, New York: Wiley-Liss, Inc.

Kleschevnikov, A. M., Belichenko, P. V., Villar, A. J., Epstein, C. J., Malenka, R. C., & Mobley, W. C. (2004). Hippocampal Long-Term Potentiation Suppressed by Increased Inhibition in the Ts65Dn Mouse, a Genetic Model of Down Syndrome. *Journal of Neuroscience*, *24*(37).

Kuriki, S., Kobayashi, Y., Kobayashi, T., Tanaka, K., & Uchikawa, Y. (2013). Steady-state MEG responses elicited by a sequence of amplitude-modulated short tones of different carrier frequencies. *Hearing Research*, *296*, 25–35. https://doi.org/10.1016/j.heares.2012.11.002

Kwon, J. S., O'Donnell, B. F., Wallenstein, G. V., Greene, R. W., Hirayasu, Y., Nestor, P. G., … McCarley, R. W. (1999). Gamma Frequency–Range Abnormalities to Auditory Stimulation in Schizophrenia. *Archives of General Psychiatry*, *56*(11), 1001. https://doi.org/10.1001/archpsyc.56.11.1001

Lachaux, J., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring Phase Synchrony in Brain Signals, *208*, 194–208.

Lee, N.-C., Chien, Y.-H., & Hwu, W.-L. (2016). Integrated care for Down syndrome. *Congenital Anomalies*, *56*(3), 104–106. https://doi.org/10.1111/cga.12159

Lehmann, A., Arias, D. J., & Schonwiesner, M. (2016). TRACING THE NEURAL BASIS OF AUDITORY ENTRAINMENT, *337*, 306–314. https://doi.org/10.1016/j.neuroscience.2016.09.011

Lehmann, K., Steinecke, A., & Bolz, J. (2012). GABA through the Ages: Regulation of Cortical Function and Plasticity by Inhibitory Interneurons. *Neural Plasticity*, *2012*, 1–11. https://doi.org/10.1155/2012/892784

Lins, O. G., & Picton, T. W. (1995). Auditory steady-state responses to multiple simultaneous stimuli. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *96*(5), 420–432. https://doi.org/10.1016/0168-5597(95)00048-W

Llinás, R. (2003). Consciousness and the thalamocortical loop. *International Congress Series*, *1250*, 409–416. https://doi.org/10.1016/S0531-5131(03)01067-7

Lott, I. T., Head, E., Doran, E., & Busciglio, J. (2006). Beta-amyloid, oxidative stress and down syndrome. *Current Alzheimer Research*, *3*(5), 521–8.

Mäkelä, J. ., & Hari, R. (1987). Evidence for cortical origin of the 40 Hz auditory evoked response in man. *Electroencephalography and Clinical Neurophysiology*, *66*(6), 539–546. https://doi.org/10.1016/0013-4694(87)90101-5

Mann, H. B., & Whitney, D. R. (1947). On a Test of Whether one of Two Random Variables is Stochastically Larger than the Other. *The Annals of Mathematical Statistics*, *18*(1), 50–60. https://doi.org/10.1214/aoms/1177730491

Mattout, J., Henson, R. N., & Friston, K. J. (2007). Canonical source reconstruction for MEG. *Computational Intelligence and Neuroscience*, *2007*, 67613. https://doi.org/10.1155/2007/67613

Mayo Clinic Staff. (2014). Down syndrome.

McCreery, R. W., Kaminski, J., Beauchaine, K., Lenzen, N., Simms, K., & Gorga, M. P. (2014). The Impact of Degree of Hearing Loss on Auditory Brainstem Response Predictions of Behavioral Thresholds. *Ear and Hearing*, (October 2015), 1–11. https://doi.org/10.1097/AUD.0000000000000120

Moore, D., Oates, J., Hobson, R., & Goodwin, J. (2002). Cognitive and social factors in the development of infants with Down syndrome. *Down Syndrome Research and Practice*, *8*(2), 43–52. https://doi.org/10.3104/reviews.129

Muthukumaraswamy, S. D., Edden, R. a E., Jones, D. K., Swettenham, J. B., & Singh, K. D. (2009). Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(20), 8356–8361. https://doi.org/10.1073/pnas.0900728106

Northoff, G., & Sibille, E. (2014). Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. *Molecular Psychiatry*, *19*(9), 966–77. https://doi.org/10.1038/mp.2014.68

O'Donnell, B. F., Vohs, J. L., Krishnan, G. P., Rass, O., Hetrick, W. P., & Morzorati, S. L. (2013). The auditory steady-state response (ASSR): a translational biomarker for schizophrenia. *Supplements to Clinical Neurophysiology*, *62*, 101–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24053034

Oda, Y., Onitsuka, T., Tsuchimoto, R., Hirano, S., Oribe, N., Ueno, T., … Kanba, S. (2012). Gamma Band Neural Synchronization Deficits for Auditory Steady State Responses in Bipolar Disorder Patients, *7*(7), 1–8. https://doi.org/10.1371/journal.pone.0039955

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. (2011). FieldTrip : Open Source Software for Advanced Analysis of MEG , EEG , and Invasive Electrophysiological Data, *2011*. https://doi.org/10.1155/2011/156869

Osipova, D., Pekkonen, E., & Ahveninen, J. (2006). Enhanced magnetic auditory steady-state response in early Alzheimer's disease. *Clinical Neurophysiology*, *117*(9), 1990–1995. https://doi.org/10.1016/j.clinph.2006.05.034

Pauli-Magnus, D., Hoch, G., Strenzke, N., Anderson, S., Jentsch, T. J., & Moser, T. (2007). Detection and differentiation of sensorineural hearing loss in mice using auditory steady-state responses and transient auditory brainstem responses. *Neuroscience*, *149*(3), 673–684. https://doi.org/10.1016/j.neuroscience.2007.08.010

Pearlson, G. D., Breiter, S. N., Aylward, E. H., Warren, a C., Grygorcewicz, M., Frangou, S., … Pulsifer, M. B. (1998). MRI brain changes in subjects with Down syndrome with and without dementia. *Developmental Medicine and Child Neurology*, *40*(5), 326–34. https://doi.org/10.1111/j.1469-8749.1998.tb15384.x

Pekkonen, E., Osipova, D., Sauna-Aho, O., & Arvio, M. (2007). Delayed auditory processing underlying stimulus detection in Down syndrome. *NeuroImage*, *35*(4), 1547–1550. https://doi.org/10.1016/j.neuroimage.2007.01.036

Picton, T. (2010). *Human auditory evoked potentials*.

Pinter, J. D., Eliez, S., Schmitt, J. E., Capone, G. T., & Reiss, A. L. (2001). Neuroanatomy of Down's Syndrome: A High-Resolution MRI Study. *American Journal of Psychiatry*, *158*(10), 1659–1665. https://doi.org/10.1176/appi.ajp.158.10.1659

Pizzarelli, R., & Cherubini, E. (2011). Alterations of GABAergic signaling in autism spectrum disorders. *Neural Plasticity*, *2011*, 297153. https://doi.org/10.1155/2011/297153

Pizzella, V., Marzetti, L., Della Penna, S., de Pasquale, F., Zappasodi, F., & Romani, G. L. (2014). Magnetoencephalography in the study of brain dynamics. *Functional Neurology*, *29*(4), 241–53.

Plourde, G., Stapelles, D. R., & Picton, T. W. (1991). The human auditory steady--state evoked potentials. *Acta Oto--Laryngologica (Supplement)*, *491*(8), 153–160.

Popescu, M., Popescu, E. A., Chan, T., Blunt, S. D., & Lewine, J. D. (2008). Spatio-temporal reconstruction of bilateral auditory steady-state responses using MEG beamformers. *IEEE Transactions on Biomedical Engineering*, *55*(3), 1092–1102. https://doi.org/10.1109/TBME.2007.906504

Port, R. G., Edgar, J. C., Ku, M., Bloy, L., Murray, R., Blaskey, L., … Roberts, T. P. L. (2016). Maturation of auditory neural processes in autism spectrum disorder - A longitudinal MEG study. *NeuroImage. Clinical*, *11*, 566–77. https://doi.org/10.1016/j.nicl.2016.03.021

Port, R. G., Gaetz, W., Bloy, L., Wang, D. J., Blaskey, L., Kuschner, E. S., … Roberts, T. P. L. (2016). Exploring the relationship between cortical GABA concentrations, auditory gamma-band responses and development in ASD: Evidence for an altered maturational trajectory in ASD. *Autism Research*, 1–15. https://doi.org/10.1002/aur.1686

Powell, D., Caban-Holt, A., Jicha, G., Robertson, W., Davis, R., Gold, B. T., … Head, E. (2014). Frontal white matter integrity in adults with Down syndrome with and without dementia. *Neurobiology of Aging*, *35*(7), 1562–9. https://doi.org/10.1016/j.neurobiolaging.2014.01.137

Presacco, A., Bohórquez, J., Yavuz, E., & Özdamar, Ö. (2010). Auditory steady-state responses to 40-Hz click trains: Relationship to middle latency, gamma band and beta band responses studied with deconvolution. *Clinical Neurophysiology*, *121*(9), 1540–1550. https://doi.org/10.1016/j.clinph.2010.03.020

Proudfoot, M., Woolrich, M. W., Nobre, A. C., & Turner, M. R. (2014). Magnetoencephalography. *Practical Neurology*, *14*(5), 336–343. https://doi.org/10.1136/practneurol-2013-000768

Quraan, M. A., & Cheyne, D. (2010). Reconstruction of correlated brain activity with adaptive spatial filters in MEG. *NeuroImage*, *49*(3), 2387–2400. https://doi.org/10.1016/j.neuroimage.2009.10.012

Ribary, U., Ioannides, A. A., Singh, K. D., Hasson, R., Bolton, J. P. R., Lado, F., … Llinas, A. R. (1991). Magnetic Field Tomography of Coherent Thalamocortical 40-Hz Oscillations in Humans. *Source: Proceedings of the National Academy of Sciences of the United States of America*, *88*(88), 11037–11041. Retrieved from http://www.jstor.org/stable/2359178

Roberts, L. E., Young, A., Bosnyak, D. J., Cheung, T., Lei, J., & Bell, K. (2007). Auditory cortical development charted by transient and 40-Hz steady-state responses in typical children and in Down syndrome. *International Congress Series*. https://doi.org/10.1016/j.ics.2007.01.043

Rojas, D. C., Becker, K. M., & Wilson, L. B. (2015). Magnetic Resonance Spectroscopy Studies of Glutamate and GABA in Autism : Implications for Excitation-Inhibition Imbalance Theory, 46–57. https://doi.org/10.1007/s40474-014-0032-4

Rojas, D. C., & Wilson, L. B. (2014). γ-band abnormalities as markers of autism spectrum disorders. *Biomarkers in Medicine*, *8*(3), 353–68. https://doi.org/10.2217/bmm.14.15

Ross, B. (2008). A Novel Type of Auditory Responses: Temporal Dynamics of 40-Hz Steady-State Responses Induced by Changes in Sound Localization. *Journal of Neurophysiology*, *100*(3), 1265–1277. https://doi.org/10.1152/jn.00048.2008

Ross, B., Herdman, A. T., & Pantev, C. (n.d.). Stimulus Induced Desynchronization of Human Auditory 40-Hz Steady-State Responses. https://doi.org/10.1152/jn.00469.2005

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, *2*(5), 255–267. https://doi.org/10.1034/j.1601-183X.2003.00037.x

Shaw, M. E., Hämäläinen, M. S., & Gutschalk, A. (2013). NeuroImage How anatomical asymmetry of human auditory cortex can lead to a rightward bias in auditory evoked fi elds. *NeuroImage*, *74*, 22–29. https://doi.org/10.1016/j.neuroimage.2013.02.002

Singer, W. (2010). Temporal Coherence: A Versatile Code for the Definition of Relations. *The Senses: A Comprehensive Reference*, *2*, 1–9. https://doi.org/10.1016/B978-012370880-9.00287-5

Sivarao, D. V, Chen, P., Senapati, A., Yang, Y., Fernandes, A., Benitex, Y., … Ahlijanian, M. K. (2016). 40 Hz Auditory Steady-State Response Is a Pharmacodynamic Biomarker for Cortical NMDA Receptors. *Neuropsychopharmacology*, *41*(10), 2232–2240. https://doi.org/10.1038/npp.2016.17

Tavabi, K., Obleser, J., Dobel, C., & Pantev, C. (2007). Auditory evoked fields differentially encode speech features: an MEG investigation of the P50m and N100m time courses during syllable processing. *European Journal of Neuroscience*, *25*(10), 3155–3162. https://doi.org/10.1111/j.1460-9568.2007.05572.x

Tort, A. B. L., Komorowski, R., Eichenbaum, H., & Kopell, N. (2010). Measuring Phase-Amplitude Coupling Between Neuronal Oscillations of Different Frequencies. *Journal of Neurophysiology*, *104*(2), 1195–1210. https://doi.org/10.1152/jn.00106.2010

Traub, R. D., Whittington, M. A., Colling, S. B., Buzsáki, G., & Jefferys, J. G. (1996). Analysis of gamma rhythms in the rat hippocampus in vitro and in vivo. *The Journal of Physiology*, (Pt 2), 471–84.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). *Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain*. *NeuroImage* (Vol. 15). https://doi.org/10.1006/nimg.2001.0978

Uhlhaas, P. J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A., & Singer, W. (2010). Neural synchrony and the development of cortical networks. *Trends in Cognitive Sciences*, *14*(2), 72–80. https://doi.org/10.1016/j.tics.2009.12.002

Van Veen, B. D., Van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering*, *44*(9), 867–880. https://doi.org/10.1109/10.623056

Vinck, M., Oostenveld, R., van Wingerden, M., Battaglia, F., & Pennartz, C. M. A. (2011). An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *NeuroImage*, *55*(4), 1548–1565. https://doi.org/10.1016/j.neuroimage.2011.01.055

Virji-Babul, N., Moiseev, A., Cheung, T., Weeks, D. J., Cheyne, D., & Ribary, U. (2010). Neural Mechanisms Underlying Action Observation in Adults With Down Syndrome. *American Journal on Intellectual and Developmental Disabilities*, *115*(2), 113–127. https://doi.org/10.1352/1944-7588-115.2.113

Virji-Babul, N., Moiseev, A., Moiseeva, N., Sun, W., Ribary, U., & Lott, I. (2011). Altered brain dynamics during voluntary movement in individuals with Down syndrome. *NeuroReport*, *22*(7), 358–364. https://doi.org/10.1097/WNR.0b013e328346a1a0

Vohs, J. L., Chambers, R. A., Krishnan, G. P., O'Donnell, B. F., Berg, S., & Morzorati, S. L. (2010). GABAergic modulation of the 40 Hz auditory steady-state response in a rat model of schizophrenia. *The International Journal of Neuropsychopharmacology*, *13*(4), 487–97. https://doi.org/10.1017/S1461145709990307

Ward, L. M. (2003). Synchronous neural oscillations and cognitive processes. *Trends in Cognitive Sciences*, *7*(12), 553–559. https://doi.org/10.1016/j.tics.2003.10.012

Whittington, M. A., Cunningham, M. O., Lebeau, F. E. N., Racca, C., & Traub, R. D. (2010). Multiple Origins of the Cortical Gamma Rhythm, 92–106. https://doi.org/10.1002/dneu.20814

Wilson, T. W., Rojas, D. C., Reite, M. L., Teale, P. D., & Rogers, S. J. (n.d.). Children and Adolescents with Autism Exhibit Reduced MEG Steady-State Gamma Responses. https://doi.org/10.1016/j.biopsych.2006.07.002

Wisniewski, K. E., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology*, *17*(3), 278–282. https://doi.org/10.1002/ana.410170310

Ye, A. X., Leung, R. C., Sch€, C. B., Taylor, M. J., & Doesburg, S. M. (2014). Atypical Resting Synchrony in Autism Spectrum Disorder. https://doi.org/10.1002/hbm.22604

Zanin, M., & Papo, D. (2013). Efficient neural codes can lead to spurious synchronization. *Frontiers in Computational Neuroscience*, *7*, 125. https://doi.org/10.3389/fncom.2013.00125