Biological Sex as a Mediating Factor of the Auditory Mismatch Negativity

by

Erica Dawn Kew

A Thesis submitted to
Saint Mary's University, Halifax, Nova Scotia
in Partial Fulfillment of the Requirements for
the Degree of Master of Science in Applied Science

August, 2019, Halifax, Nova Scotia

Approved:	Dr. Derek Fisher Supervisor
Approved:	Dr. Jason Ivanoff Co-Supervisor
Approved:	Dr. Philip Tibbo Committee Member
Approved:	Dr. Aaron Newman Committee Member
Approved:	Dr. Anne Sophie Champod External Examiner
	Date: August 2019

Abstract

Biological Sex as a Mediating Factor of the Auditory Mismatch Negativity

By Erica Dawn Kew

Abstract: The mismatch negativity (MMN) is an EEG-derived event-related potential (ERP) elicited by any violation of a predicted auditory 'rule' and is thought to reflect updating of the stimulus context. In MMN research, sex differences have been largely underreported; the few studies that report sex-based analyses have largely focused on phonetic sounds with emotional valence, while pure-tone stimuli have not yielded any significant results. This study investigated whether sex differences could be detected in a healthy population using a 5-deviant "optimal" multi-feature paradigm (Näätanen, 2004; Experiment 1) and a complex 'missing stimulus' pattern paradigm (Salisbury, 2012; Experiment 2). The only significant difference observed was that males were found to have enhanced left-frontal MMN amplitudes compared to females when presented with the location deviant of the optimal paradigm. These results suggest that the auditory MMN may be more characterized by sex similarities.

August, 2019.

Acknowledgements

There are several people whom I wish to gratefully acknowledge, as they were instrumental in the production of this thesis. First, I would like to thank everyone from the Biomedical Translational Imaging Centre (BIOTIC) who helped contribute to the completion of this research project.

The most heartfelt gratitude goes out to my supervisor, Dr. Derek Fisher, for without him I could never have accomplished this dream. Derek, thank you for being the most encouraging, patient, and supportive mentor I could have ever asked for. You have believed in me since day one, you have pushed me to be the best student and person I can be, and you have supported my journey every step of the way. You know that it has not been an easy journey for me, with personal pain that we could never have saw coming and a maternity leave right in the middle of my degree. I can never thank you enough for your incredible support and kindness during one of the darkest periods of my life, and for not giving up on me even when I began to give up on myself. Thank you for allowing me to create my own schedule and giving me the option to work from home and spend more time with my family. I owe my entire academic career to you, as your passion for research has instilled the passion within me.

To my co-supervisor, Dr. Jason Ivanoff, for the massive role you played in helping me accomplish this dream. Thank you for your input and helping me to consider different perspectives throughout the research process. Thank you for always being understanding and kind, and for supporting me and showing compassion through a difficult time in my life. To my remaining committee members, Dr. Philip Tibbo and Dr. Aaron Newman, thank you for agreeing to sit on my thesis committee and provide your expertise. I appreciate all you have taught me and your contribution to this research.

I wish to acknowledge all of the participants who contributed their time and effort this research. Thank you for your contribution to advancing science research. Special thanks to Hayley Riel and Catrina MacPhee, for your work with recruiting participants and collecting data while I was on maternity leave.

To everyone who works in our lab, you're all rockstars and I have so much respect for all of you. Special thanks to Jenna Bissonnette, Kaitlin Napier for always letting me bounce ideas off of you, for letting me vent about my frustrations, and for getting me out of the lab to eat lunch, share some laughs and making me feel welcome in your lives. Thank you for just always being such a joy to be around.

To my lab mama, Donna Thompson, you are the reason I am here. Before we even had a personal relationship, you pushed me to believe in myself. You are a beautiful soul and have been one of my biggest supporters since day one. Another special thanks to Marisa Grant, for always being an advocate for my mental health and for providing so much support for me over the years, both in my academic and personal life. Thank you both, for being amazing role models to the type of woman I hope to be. I am eternally grateful for having both of you in my lives and I consider myself lucky to be able to call you my friends.

To my entire Masonview family, thank you for supporting my decision to go back to school and allowing me to put my studies first to accomplish this goal.

To my mother, the person who without a doubt is the reason for my strength. Thank you for helping me to find that strength at moments where I thought it was lost. Thank you for answering every call, and listening to every rant, and sometimes just sitting on the phone in silence when I was overwhelmed and didn't know what to say. Thank you for always offering your continuous love and support. Thank you for all of the long days where you took such good care of Roan while I could not be around. I appreciate you so much, and our little family is so grateful for you.

To my brother, Kyle. Thank you for always being there through these last few years, and for forcing me out of the house, for the trail walks, trips to the park, or just a coffee. I am so proud to be your sister, and I'm so grateful for our friendship. Ps. Lafarge.

To my adored niece, Rylea, six years ago you came into this world and you haven't stopped teaching me lessons ever since. You have a very special place in my heart, and having you look up to me has been one of my greatest motivations to never give up and to always do the right thing. I hope that you are as proud of me as I am of you.

Thank you to the rest of my family for believing in me. Thank you to my Dad for always being so present in my life even being a province away, you are so special to me and I am so lucky to have your unconditional love and support. Thank you to my step-mom for being so proud of my decision to go back to grad school, and for always bragging about my accomplishments, I appreciate you. Thank you to my sister, Allison, who is such an amazing role model and who is a big part of the reason I wanted to continue on to grad school. Alli, you have paved a path of greatness in our family and I am proud to follow in your academic footsteps. Thank you to my brother, Drew, for your love and for always being able to make me laugh even during the hard times.

My most important thanks is for my beloved husband, James. You have been my rock through this entire process. The appreciation I have for you and our life together is endless. Thank you from the bottom of my heart for not only encouraging me to go back to school, but for supporting all of the long days and nights away from our family. Thank you for always packing me lunches and making sure I was taking care of myself. Thank you for always encouraging me, for always telling me how awesome you think I am, and for believing in me when I didn't believe in myself.

And finally, to my two beautiful children, Willow and Roan, thank you for changing my life in the best ways possible, thank you for keeping me grounded when I questioned this journey, and thank you for being my constant motivation to be the best person and mother that I can be. You two are the biggest reason I have not faltered along this journey. My only hope in the world is to make you proud. I love you so much.

Halifax, June 2019.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Biological Sex as a Mediating Factor of the Auditory Mismatch Negativity

CHAPTER 1: GENERAL INTRODUCTION

1.1. Event-Related Potentials: An Overview

Within the fields of attention and information processing, electroencephalographically (EEG)-derived event-related potentials (ERPs) provide an exquisitely sensitive method of indexing cognition that can both complement and clarify behavioural observations. The ERP waveform is elicited in response to a specific stimulus, such as tones or light flashes, or cognitive events, such as recognition, decision making or response to specific stimulus events. Specifically, ERPs represent the characteristic neural activity that follows the presentation of a stimulus. They are extracted from recorded brain activity by averaging multiple EEG windows (called an epoch) that is time-locked to a specific stimulus or behavioural event, resulting in the random background noise of the EEG cancelling to zero, leaving behind a constant and invariant waveform. When recorded concurrently with behavioural measures of task performance, ERPs provide a more complete picture of the cognitive features underlying different arousal, mood and psychiatric states. The averaged ERP plots voltage (microvolts: μV) as a function of time (milliseconds: ms), with the resulting waveform appearing as a series of deflections or peaks. Conventionally, these components are described in terms of polarity (positive peaks labeled P; negative peaks labeled N), and sequence (ordinal position of peak) or peak latency of where the ERP typically occurs (Rugg & Coles, 1995). In this manner, the third positive peak in the waveform may be labeled the P3 or the P300, as it is expected to occur approximately 300 ms after stimulus onset.

Classification of ERPs is generally divided into two types: the early-occurring

exogenous components, and the later endogenous components. The exogenous ERPs are generally those occurring within 100 ms of stimulus onset and are so named because their respective amplitudes and latencies are primarily determined by the properties of the eliciting stimulus, such as intensity and rate (Friedman & Squires-Wheeler, 1994). As such, they are relatively insensitive to psychological variables such as mood and attention (Roth, 1977). These ERPs are mainly generated in the primary sensory cortex and association areas of the brain (Chiappa, 1990). By contrast, the endogenous ERP components (latency > 100ms) are highly influenced by cognitive and psychological variables manifest upon the subject and are relatively independent of eliciting stimulus physical characteristics (Pritchard, 1986).

ERPs are regularly used in psychological research because they can provide valuable insights into basic cognitive mechanisms as well as higher brain functioning well before the performance of an overt response (van der Stelt & Belger, 2007). Not only can ERPs help disentangle stimulus evaluation from response selection and execution processes, but certain ERPs are indices of automatic sensory perception that do not require any behavioural response from an individual and may not require the individual's attention to the stimuli at all (Näätänen, 2003). Furthermore, ERPs provide a temporal resolution far superior to some of the more sophisticated imaging techniques (i.e. PET, fMRI), making this methodology more suitable for capturing rapid changes in information processes, such as auditory change detection.

Within auditory cortical function there are several different types of auditory waveforms; the P50 waveform occurs approximately 50 ms after stimulus onset (Boutros, Zouridakis, Rustin, Peabody, & Warner, 1993) and acts as an index of sensory gating

(Potter, Summerfelt, Gold, & Buchanen, 2006); the N100 waveform occurs between 90-200 ms following stimulus onset and represents an orienting response that matches the presentation of an auditory stimulus with previously experiences stimuli (Sur & Sinha, 2009); the P300 waveform occurs approximately 300 ms following stimulus onset and is elicited in the process of decision making by inserting unique and highly salient (novel) stimuli in the pattern of repeated standard stimuli. The P300 can be divided into two subcomponents: the classic P300 (P3a) and the novelty P300 (P3b) (Polich, 2007). The P3a is elicited by deviant stimuli that are irrelevant for the task while being more noticeable than the targets, and the P3b is elicited by deviant stimuli that are relevant and attended to (Linden, 2005). Finally, the N200 waveform occurs approximately 200 ms following stimulus onset and creates a negative deflection (Patel & Azzam, 2005). The N200 can be divided into three components: the N2a, N2b, and N2c. The N2b occurs due to a change in the physical property of a stimulus (Sur & Sinha, 2009) and the N2c occurs during classification tasks (Pritchard, Shappell, & Brandt, 1991). The N2a, which is commonly referred to as the mismatch negativity (MMN), is the waveform we will focus on in this thesis and will be discussed in detail below.

1.2. Mismatch Negativity

The MMN is an ERP that can be elicited automatically and pre-attentively (Näätänen, 1990). Auditory change detection is indexed by the MMN (Näätanen et al., 2012), which has been used as a marker of basic central auditory function; this has important “real world” applications; incorrect organization of sensory stimulation from the surrounding environment may result in dysfunction of later sensory processes and difficulty initiating appropriate responses when necessary (Jahshan et al., 2012). The

automatic and pre-attentive MMN is commonly generated by randomly inserting rare deviant sounds that may differ in many ways including frequency, duration, intensity, and/or location, into a train of repeating standard sounds (Näätänen & Alho, 1997). The older memory trace model of MMN posits that before detecting auditory change, the central auditory system first forms a sensory memory representation of the expected sound (or groups of sounds), and then uses this representation to compare against other incoming sounds; the MMN is generated when an incoming deviant does not match the representation, sending a signal to the executive mechanisms and interrupting current cognitive processes in order to shift attention towards the deviant sounds (Näätänen, Paavilainen, Rinne, & Alho, 2007). A newer prediction error model suggests that the auditory cortex derives a prediction of the auditory environment based on sensory stimulation and that deviations from this prediction elicit an error signal from primary to secondary cortices used to adjust the model (Winkler & Czigler, 2012). The error prediction model better explains how MMN can be elicited by violations of an abstract rule, such as omission of a sound in a pattern, which may relate only to the relationship between sounds, and how, in certain cases, MMN may be elicited by a repeated tone or the absence of an expected tone. The MMN typically occurs 100-250 ms following the onset of these deviant stimuli, and is superimposed upon obligatory sensory processes until isolated in a difference wave (a point-by-point subtraction of the standard stimulus waveform from the ERP to the deviant stimulus) (Näätänen, 1982). The resulting waveform is a negative peak with a frontal-topography maximum amplitude (Schröger, 2007).

1.3. MMN Evocation

Evocation of the MMN is most simply illustrated in the framework of the classic oddball paradigm, in which a homogenous sequence of identical repeated stimuli is interrupted at random and unpredictable times by a deviant stimulus possessing an altered physical or temporal feature (e.g. duration, pitch, intensity). In this classic oddball paradigm, only one type of MMN can be obtained at a time, causing very long procedure times when more than one deviant needs to be recorded. Näätänen and colleagues (2004) proposed a new, multi-feature paradigm that presented five types of deviants in the same stimulus block. The MMNs obtained in this new paradigm were equal in amplitude to those in the traditional oddball MMN paradigm (Näätänen et al., 2004), as such this new paradigm was referred to as the "optimal" MMN paradigm since it can record multiple MMNs in the same recording session. There has been some criticism however, that these simple stimulus-change paradigms may not elicit a true MMN. Jacobsen and Schröger (2001) suggested that the MMN that is typically measured in oddball paradigms with frequency deviants contains both the MMN and an overlapping N100 enhancement; as the deviant stimulus is presented much less than the standard, the N100 elicited by deviant tones is much larger than the refractory response that is evoked by standard tones, and the difference in their amplitudes is retained in the difference wave. In such cases, the MMN and N100 can overlap and summate, and unravelling their relative contributions to the difference wave is often not possible without careful control procedures, such as using the same sounds as both standard and deviant in subsequent experiments (Schirmer et al., 2008). In response to these concerns, pattern paradigms were explored which would probe higher order processes that the optimal paradigms does

not. One such complex pattern MMN paradigm was developed by Salisbury (2012). Based on the Gestalt principle of grouping by proximity, the paradigm is unique because its mismatch is the absence of a sound rather than the presentation of a new one. Using only one repeated tone, 330 ms apart, in groups of 6 separated by a 750 ms inter-trial interval, MMN was elicited by a missing 4^{th} or 6^{th} tone based on a violation of expectancy for a group of six stimuli that has been developed by primitive auditory intelligence. While the complex pattern MMN paradigm has been validated in healthy populations, one potential moderating factor that has not yet been investigated is biological sex.

1.4. Sex Differences in Brain Research

In the past, sex differences were ignored in brain research due to the idea that males and females only differed reproductively (Harris, 1948; Young, Goy, & Phoenix, 1964), or females were excluded altogether because of the inconvenience of controlling for menstrual cycles (Petersen, Kilpatrick, Goharzad, & Cahill, 2014). Researchers began to move away from the narrow reproductive parameters as more studies began to report sex differences (Gupta et al., 2017; McCarthy, Nugent, & Lenz, 2017). These differences can be partly explained by sex hormones, once thought to only affect reproductive organs but have since been found to act through the brain (among other areas) of both males and females (Herting et al., 2014). They have been found to act through many cellular and molecular processes that can alter the brain's structure and function, influence behaviour, and provide neuroprotection. Functions such as mood, blood pressure regulation, motor coordination, and opioid sensitivity, which were not previously regarded to have sex differences, have been found to be developmentally programmed by sex hormones

(McEwen & Milner, 2017).

In the earliest stages of life it is determined whether a fetus will have two X chromosomes (female) or X and Y chromosomes (male), and this distinction determines how their underlying neurochemical and molecular mechanisms will differ. There are many important and significant sex differences within these mechanisms, however in most cases, sex differences are much more subtle (Joel & Tarrasch, 2014). This can lead to conflicting conclusions and controversy surrounding which patterns of connectivity and brain regional differences are involved, and how much confidence researchers have in their conclusions of these sex differences. Sex differences have been found to emerge throughout the entire lifespan, through both genetic and epigenetic mechanisms (McEwen & Milner, 2017), and some examples will be discussed below.

1.3.1. Sex differences in brain anatomy.

Female and male brains are overwhelmingly more similar than they are different, and those sex differences in brain anatomy that do exist have been found to vary depending on the age of the population (Giedd, Raznahan, Mills, & Lenroot, 2012). The most consistently reported sex difference in brain anatomy is of brain size, with male brains measuring 10% larger than female brains across all age populations (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Goldstein et al., 2011; Reiss, Abrms, Singer, Ross, & Denckla, 1996) and even post-mortem data (Witelson, Beresh, & Kigar, 2006). The female brain tends to peak in size at 10.5 years while the size of male brains peak much later at 14.5 years (Giedd et al., 2012). Similarly, the volume of the cerebellum, the posterior brain structure involved in many brain processes such as motor control and emotional processing (Riva & Giorgi, 2000), has been found to be

consistently 10-13% larger in males, peaking around 15.6 years, while female cerebellum volume peaks much earlier at 11.8 years (Tiemeier, Lenroot, Greenstein, Tran, Pierson, & Giedd, 2010). The overall size of the caudate, involved in movement and attention (Sowell, Trauner, Gamst, & Jernigan, 2002), has been reported as proportionately larger in females than males, although numbers vary depending on participant ages and methodology (Filipek, Richelme, Kennedy, & Caviness, 1994; Giedd et al., 1997; Paus, 2010; Sowell et al., 2002). This is interesting given that researchers have found reduced caudate volumes in male predominant disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and Tourette's syndrome (Giedd, Shaw, Wallace, Gogtay, & Lenroot, 2006).

Sex differences can be seen in gray matter volume as well as the neurodevelopmental trajectories of cortical gray matter (Lenroot et al., 2007). Males have been found to have 9-14% larger overall volumes of cortical gray matter than females (Lenroot et al., 2007), which makes it interesting that females have been found to have a larger volume of gray matter than males in a number of different brain structures, including the caudate, left superior temporal gyrus, and the left superior frontal gyrus (Luders, Gaser, Narr, & Toga, 2009). The parietal lobe, while presenting more sex similarities than differences in structure, has been found to significantly decrease in surface area across development in females, while remaining consistent in males throughout the lifespan (Salinas, Mills, Conrad, Koscik, Andreasen, & Nopoulos, 2012). While sex differences in gray matter remain relatively consistent across the lifespan, sex differences in white matter increase as age increases (Paus, 2010). White matter has been found to develop at a greater rate in males than females, resulting in increasingly larger

white matter volumes than females as age increases (De Bellis et al., 2001; Lenroot er al., 2007). These sex differences in brain structure almost certainly influence cognition, which is discussed below.

1.3.2. Sex differences in cognition.

There is compelling evidence that sex hormones are a major influence in the organization and maintenance of sex differences in cognition (Kimura, 2006), and that these differences are present at a very early age (Satterthwaite et al., 2015). Males are commonly found to be superior at visuospatial and motor tasks (Gur et al., 2012; Voyer, Voyer, & Bryden, 1995), and have been found to outperform females on arithmetic computation and arithmetical reasoning, which are mediated by male advantages in computational fluency and spatial recognition (Geary, 2000). In contrast, females are commonly found to be superior in areas related to social cognition and recognition memory (Gur et al., 2012), as well as episodic memory (Herlitz, Nilsson, & Bäckman, 1997), verbal production (Hyde & Linn, 1988) and verbal processing (Lewin, Wolgers, & Herlitz, 2001). These sex differences may be due to differential connectivity between males and females; from as young as nine years of age, males have been found to have greater between-module connectivity while females have been found to have more within-module connections, suggesting that female brains are more functionally segregated than males (Satterthwaite et al., 2015).

1.3.3. Sex differences in emotion.

Females have been found to be more responsive to emotional stimuli than males (Domes et al., 2009), and self-report studies investigating sex differences in emotion have found females to show greater emotional abilities than males when it comes to different

areas, such as expression (Kring & Gordon, 1998) or awareness (Feldman Barrett, Lane, Sechrest, & Schwartz, 2000). One study (Fischer, Rodriguez Mosquera, Vianen, & Manstead, 2004) found no significant differences between sexes with regards to self-reported emotional intensity, but did find that the two sexes differed on the number of times they self-reported feeling emotions regarded as powerful (e.g., anger) vs powerless (e.g., sadness). Males were found to report more powerful emotions while females were found to report more powerless emotions, however the intensity at which the two sexes experienced these emotions was not statistically different (Fischer et al., 2004). The questions raised from these sex differences are difficult to explain without knowing the brain mechanisms that are contributing to these sex differences, so researchers have stressed the importance of brain imaging techniques, such as fMRI or PET, to visually locate where these emotional sex differences are occurring in the brain.

Brain imaging studies are elucidating the specific regions involved with specific emotions or the processes that characterize, amplify, change, or maintain emotional states (Goldstein, 2006). Significant sex differences in brain activity have been demonstrated regarding memory for negative emotional material and inducing negative emotions, with women demonstrating greater aversive cues than men (Asthana and Mandal, 1998). As well, sex differences in laterality effects have been found for emotional processing in general. Females are found to show enhanced activity of the amygdala in response to negative pictures (Domes et al., 2009), greater and more significant brain activity in the anterior cingulate gyrus, left insula, and right orbitofrontal cortex when expressing negative vs positive emotions (George, Ketter, Parekh, Herscovitch, & Post, 1996), and greater brain activity in the left anterior insula for mood induction in general (Damasio et

al, 2000).

1.3.4. Sex differences in pain.

Important sex differences exist at all levels in the signalling systems involved in pain processing, suggesting sex differences in the operation of pain mechanisms (Cahill, 2006), including potentially different signaling pathways (Sorge et al., 2015), as well as behavioural responses to pain (Bartley & Fillingim, 2013). Associative learning related to pain is mediated in part by the cerebellum, and there is a difference seen in the functional connectivity in cerebellar lobules between males and females; female's lobules represent mostly somatomotor networks while male's lobules show enhanced neural activation that is representative of frontoparietal and ventral attention networks (Labrenz, Icenhour, Benson, & Elsenbruch, 2015).

In chronic pain conditions, such as irritable bowel syndrome (IBS), allodynia (a form of pain hypersensitivity), and migraines, females tend to have a higher prevalence than males (Gupta et al., 2017; Labrenz et al., 2015; Sorge et al., 2015), which could be due to the sex differences seen in the cerebellum and its involvement in associative learning processes of conditioned anticipatory safety from pain (Labrenz et al., 2015). Female chronic pain patients also show more structural and functional alterations in primary sensorimotor cortices than male chronic pain patients (Gupta et al., 2017).

Pain mediation can also be dependent on biological sex, as pain reduction medications, such as morphine (Loyd & Murphy, 2014) and microglial inhibitors (Sorge et al., 2015) are less potent in females than males in alleviating pain. Sorge and colleagues (2015) argued that this sex-specific response depends on testosterone levels.

1.3.5. Sex differences in psychiatric illness.

Developmental brain conditions such as autism, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, stuttering, and dyslexia, are more common in males than females (McCarthy et al., 2017). Males are four to five times more likely to develop autism and experience more social impairments than females who develop autism (Halladay et al., 2015). Males are two to three times more likely to develop ADHD, and experience more hyperactivity, externalizing and impulsivity than females, while females experience more internalizing, inattention and intellectual impairment than males (Arcia & Conners, 1998; Gaub & Carlson, 1997). Males are three times more likely to develop oppositional defiant disorder or conduct disorder, and will experience earlier onset and more externalizing symptoms than females (Loeber, Burke, Lahey, Winters & Zera, 2000; Trepat & Ezpeleta, 2011). Finally, stuttering is also found to occur twice as often in males than females, with adolescent onset being four times higher in males (Craig, Hancock, Tran, Craig & Peters, 2002).

While males are generally more likely to develop neurological developmental conditions, most neuropsychiatric conditions are found to be more common in females with the exceptions of alcoholism (or substance abuse) and schizophrenia (McCarthy et al., 2017). Females are two times more likely to have a major depressive disorder (Kessler, 2003), post traumatic stress disorder (PTSD; Breslau, Davis, Andreski, Peterson, & Schultz, 1997), and/or generalized anxiety disorder than males (McLean, Asnaani, Litz, & Hofmann, 2011); are 2.5 times more likely to have a panic disorder than males (McLean et al., 2011); 1.5 times more likely to have obsessive compulsive disorder (OCD) than males (Bogetto, Venturello, Albert, Maina, & Ravizza, 1999); three or four

times more likely to develop an eating disorder such as anorexia nervosa or bulimia (Hudson, Hiripi, Pope, & Kessler, 2007; Raevuori, Keski-Rahkonen, & Hoek, 2014); and are more likely to develop bipolar II than males (though males experience earlier onset than females; Arnold, 2003). As mentioned above, alcohol or substance abuse is more commonly found among males than females, however females typically experience earlier onset and progress to addiction more quickly than males (Ceylan-Isik, McBride, & Ren, 2010). Additionally, schizophrenia is a very complex brain disease that has a higher prevalence and earlier onset in males (Aleman, Kahn, & Selten, 2003), with more language disruption (Walder et al., 2006), positive symptoms (e.g. hallucinations and/or delusions), and a more severe course of illness and prognosis than females (Bergen et al., 2014). Early-onset schizophrenia is diagnosed when symptoms begin in childhood or adolescence (normally prior to age 16) and late-onset schizophrenia is diagnosed when symptoms appear after the age of 45. Males are more likely to develop early-onset schizophrenia than females, while females are more likely to develop late-onset schizophrenia than males (Aleman et al., 2003).

Neurodegenerative or autoimmune diseases are not as consistent in regards to sex differences, compared to neurodevelopmental and neuropsychiatric conditions. While multiple sclerosis (MS) and Alzheimer's disease are more commonly found in females, Parkinson's disease and amyotrophic lateral sclerosis (ALS) are more commonly found in males (McCarthy et al., 2017). Females are two times more likely to develop MS (with the exception of primary progressive MS) and experience earlier onset than males (Orton et al., 2006), however, males will typically experience a more severe form of MS than females (Beeson, 1994). Females are 2 times more likely to develop Alzheimer's disease

and experience earlier onset than males (Barnes, Wilson, Bienias, Schneider, Evans, & Bennett, 2005). Males are 1.5 times more likely to develop Parkinson's disease and three times more likely to develop ALS than females, and typically have an earlier onset for both diseases when compared to females (Haaxma et al., 2007; McCombe & Henderson, 2010).

1.5. MMN and Sex Differences

In MMN research, sex differences have been largely underreported, with the few studies that report sex-based analyses having largely focused on emotional or phonetic stimuli where the standard and deviants are made up of phonetic sounds with emotional valence rather than pure tones. Phonetic MMN studies have found females to have larger MMN amplitudes when compared to males; Aerts, Van Mierlo, Hartsuiker, Santens, and De Letter (2015) investigated sex differences using the phoneme /b/ as the standard sound and phonemes /g/, /p/, and /m/ as the deviant sounds. Participants were instructed to ignore the auditory stimuli and to focus their attention on a silent movie. Auditory phoneme discrimination found MMN amplitudes of females to be significantly greater than the MMN amplitudes of males, while MMN latencies were found to be significantly shorter in females compared to males (Aerts et al., 2015). Fan, Hsu, and Cheng (2013) compared the vocal sound "dada" to an acoustically matched non-vocal sound and found MMN amplitudes to be significantly greater in females than males with the vocal sound, but no difference was found for the non-vocal sound. Similarly, Hung and Cheng (2014) used the same vocal sound "dada" but presented it to participants in three different emotional tones: fearful, happy, and neutral, along with an acoustically matched non-vocal sound. MMN amplitudes were found to be significantly higher in females than

males for the vocal sounds, specifically the fearful tone, but no difference was found for the non-vocal sound (Hung & Cheng, 2014).

Areas related to phonological and sub-lexical processes, such as Broca's area and the superior temporal cortex have been found to be proportionally larger in females than males (Harasty, Double, Halliday, Kril & McRitchie, 1997), and females have been found to have increased cortical thickness in posterior temporal regions (Sowell et al., 2007) and a higher percentage of gray matter volume when compared to males (Gur et al., 1999). The increased gray matter in these key regions in women might help to explain the computational advantage females have in phonetic MMN studies, however Sowell and colleagues (2007) suggested that that the emotional side of language may play the biggest role in this sex difference due to their findings of thicker cortices most prominently in the right hemisphere (non-dominant for language).

Schirmer and colleagues (2008) considered the role estradiol, the primary female sex hormone, may have on MMN amplitudes; using the vocal sound "dada" presented in two different emotional tones: very angry and neutral, researchers measured estradiol levels and MMN amplitudes. Female MMN amplitudes were found to be significantly larger than those of males when the emotional tone presented was very angry. No difference was found between the two sexes in regards to the neutral emotional tone, and only females showed a significantly smaller MMN amplitude to the neutral emotional tone when compared to the very angry emotional tone. The authors found that estradiol is associated with listener sensitivity to the unattended and unexpected change in speaker prosody that MMN is elicited by, and that estradiol may directly or indirectly reduce sensitivity to neutral (unemotional) information (Schimer et al., 2008).

In most cases, pure tone MMN studies yield similar results to emotionally neutral or non-vocal sounds, often finding no significant differences between sexes. There have been reports of sex differences in healthy populations, but only with regards to visual stimuli; Yang et al. (2016) investigated sex differences in pre-attentive processing of duration information using a deviant-standard reverse oddball paradigm for auditory and visual mismatch negativity. For the auditory task, participants were instructed to focus their attention on a self-selected, sub-titled, silent film while ignoring auditory stimuli presented binaurally through headphones. For the visual task, participants were instructed to focus their attention on a black cross in the center of a screen while ignoring two solid black squares that were simultaneously presented for 50 or 150 ms in the periphery of the screen. In this visual task, participants also had to press one of two buttons to indicate "big" or "small" as quickly and accurately as possible when the size of the cross changed. Results found MMN amplitudes to be significantly higher in males when compared to females during the visual MMN task, but found no difference between the two sexes during the auditory MMN task (Yang et al., 2016). Other studies investigating sex differences in auditory MMN have also been unsuccessful in finding a significant difference between female and male participants (Nagy, Potts, & Loveland, 2003; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015).

One study (Qiao et al., 2015) used auditory mismatch negativity to investigate sex differences in major depressive disorder (MDD) using a deviant-standard reverse oddball paradigm. Participants were instructed to focus their attention on a self-selected, sub-titled, silent film while ignoring auditory stimuli presented binaurally through headphones. Results found MMN amplitudes to be significantly smaller in female MDD

patients when compared to male MDD patients, however no difference was found between the two sexes in the control groups, suggesting that the sex difference in this case was due to neural changes associated with the illness. Another study (Light et al., 2015) investigated MMN in schizophrenia patients using a duration-deviant auditory oddball paradigm. The paradigm was presented to participants binaurally through headphones while they watched a silent cartoon movie, and results reported male patients had significantly smaller MMN amplitudes compared to female patients (Light et al., 2015).

It should be noted than these pure tone MMN studies have all used the traditional oddball paradigm, the most simplistic MMN paradigm that only probes basic auditory change detection function and only accounts for one of several different types of deviants. However, the optimal MMN paradigm, which presents five different types of deviants in the same stimulus block, and the complex pattern MMN paradigm, which may be more comparable to the computational complexity of the emotional MMN paradigms, may be more appropriate to investigate sex-based differences.

1.6. General Objectives

It is important to consider that the optimal (Fisher, Campbell, Abriel, Ells, Rudolph, & Tibbo, 2018; Thönnessen et al., 2008) and the complex pattern MMN paradigm (Rudolph et al., 2015) are used in psychiatric research to investigate illnesses with documented biological sex differences. Therefore, it is essential to investigate if these paradigms have sex differences in healthy populations in order to determine if biological sex has an impact on MMN in unaffected controls. Experiment 1 compared MMN data between healthy biological females and healthy biological males using the

optimal MMN paradigm. Experiment 2 compared MMN data between healthy biological females and healthy biological males using the complex pattern MMN paradigm. Based on previous research, it is hypothesized that MMN amplitudes will be significantly enhanced in biological females when compared to biological males, but only with the complex paradigm.

CHAPTER 2: MISMATCH NEGATIVITY IN FEMALES AND MALES AS MEASURED BY A MULTI-FEATURE MMN PARADIGM (Experiment 1)

2.1. Introduction

Prior to the development of the "optimal" multi-feature MMN paradigm (Näätänen et al., 2004), traditional oddball paradigms could only record one deviant at a time, so it was not easy to obtain data for multiple types of deviants with the same participants. The multi-feature MMN paradigm developed by Näätänen and colleagues (2004) is referred to as the "optimal" MMN paradigm because of its ability to record multiple MMN deviant types in the same recording session. The authors tested the multi-feature paradigm's reliability by comparing MMN amplitudes between the traditional oddball paradigm and two paradigms in which five types of deviants (different from the standard in one of the following ways: gap, pitch, location, intensity, or duration) occurred within the same sequence (denoted as "Optimum-1" and "Optimum-2"). The "Optimum-1" paradigm consisted of a sequence where every standard tone was followed by one of the five deviants and the "Optimum-2" paradigm consisted of a sequence where three standard tones were presented before one of the five deviants. In all three conditions, deviants elicited MMNs that peaked around 150 ms from stimulus onset, and MMN amplitudes were found to be largest in the "Optimum-1" condition and smallest in the "Optimum-2" condition ($p < 0.05$ for all combinations; Näätänen et al., 2004). The five-deviant "Optimum-1" paradigm obtained MMN amplitudes as large as those obtained in the traditional one-deviant oddball paradigm, albeit in a fraction of the time, leading the research team to propose this paradigm as the "optimal" MMN paradigm.

While the "optimal" MMN paradigm has been used extensively in many areas of research since it was introduced in 2004, including schizophrenia (Fisher et al., 2008;

2018), autism (Lepistö, Kujala, Vanhala, Alku, Huotilainen, & Näätänen, 2005) and dyslexia (Kujala, Lovio, Lepistö, Laasonen, & Näätänen, 2006) it has been not been used to probe sex differences in a healthy (or clinical) population. Based on previous research reporting no sex differences when pure tone stimuli are used in healthy populations (Nagy et al., 2003; Qiao et al., 2015; Tsolaki et al., 2015; Yang et al., 2016), it is hypothesized that there will not be a sex difference in regards to MMN amplitudes.

2.2. Methods

2.2.1. Participants.

Thirty-three right-handed, cis-gendered participants (18 female, 15 male) self-reporting negative psychiatric, medical, neurological and alcohol/drug abuse histories, and non-use of medications were recruited from the general public via online advertisements and word-of-mouth. Male and female participants were matched as closely as possible; no significant between-group differences were observed for age (p = .54) or National Adult Reading Test (NART; used as a proxy for intelligence) score (p = .17). See Table 1.

Table 1
Mean (± SD) age and NART scores for female and male participants (Experiment 1).

	Female	Male
Age	23.22 (4.35)	24.13 (4.00)
NART	34.22 (9.78)	38.67 (8.16)

2.2.2. ‘Optimal’ multi-feature MMN paradigm.

This study employed a multi-feature MMN paradigm, regularly used in our lab in the assessment of the MMN in schizophrenia and early-phase psychosis. The stimuli were identical to those used by Näätanen and collegues (2004). Briefly, within this paradigm every second tone is a standard (P = 0.5) and every other one is one of the five

deviants (P = 0.1 each); standard tones are made up of sinusoidal partials of 500, 1000, and 1500 Hz which are 75 ms in duration (including 5 ms rise and fall times), and the deviant tones differ from the standard tones in frequency (± 10%), duration (50 ms), intensity (± 10 dB), perceived location of sound origin (90%) or contained a gap (7 ms) in the middle of the tone. Except where stated, the deviants are identical to the standards. The stimuli was presented in 3 blocks of 5 minutes each (1845 stimuli) for a total of 15 minutes (5535 stimuli); the first 15 stimuli of each block were standards. Deviants were presented in a pseudorandomized order so that no deviant type was presented consecutively. Rest intervals of ~1 minute were inserted between each of the test blocks of the MMN paradigm. See Figure 1.

$$S - D_3 - S - D_1 - S - D_4 - S - D_2 - S - D_5 - S - D_4 - S \ldots$$

Fig 1. Schematic illustration of the "optimal" multi-feature MMN paradigm (adapted from Näätanen, 2004)

2.2.3. EEG recording and ERP computation

Electrophysiological recordings were conducted onsite at the BIOTIC Neuroimaging Research Laboratory, located at the QEII Health Sciences Centre. ERPs were extracted from EEG activity recorded from an electrode cap with active Ag^+/Ag^+-Cl^- electrodes at sixty-four sites according to the 10-10 system of electrode placement, including: three midline sites (frontal [F_z], central [C_z], parietal [P_z]); three left hemisphere (frontal [F_3], central [C_3], parietal [P_3]) and three right hemisphere (frontal [F_4], central [C_4], parietal [P_4]) scalp sites; and bilateral mastoid activity. Electrodes were also placed on the mid-forehead to serve as ground. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity was taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 10kΩ. Electrical activity was recorded with an amplifier bandpass of 0.1 and 100 Hz,

digitized at 500 Hz, and stored on hard-disk for later offline analysis.

Electrical activity was separately averaged for each stimulus type (standard and deviants) and was digitally filtered offline with a bandpass of 0.5-20 Hz. Electrical epochs (350 ms duration, beginning 50 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using an algorithm operating in the time and frequency domain (Gratton et al., 1983) and then baseline corrected using a 50 ms window of pre-stimulus activity. Those epochs with EEG or EOG voltages exceeding ± 75 μV were excluded from the analysis and the remaining artifact-free epochs were averaged according to stimulus type.

MMN difference waveforms were derived by digital point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus. MMN peaks were assessed by quantifying peak negative amplitudes (± 4 ms; relative to average pre-stimulus baseline activity) within an analysis window custom-tailored for each paradigm based on visual inspection (80-270 ms). MMN latency measurements were measured at F_z, the site of maximum amplitude.

2.2.4. Procedure

Participants attended the laboratory for one morning (9:30am-11:30am) test session, and were required to abstain from illicit drugs and alcohol beginning at midnight of the previous day. Participants were not required to abstain from tobacco-use as this could promote withdrawal symptoms that could interfere with ERP recordings. Additionally, acute nicotine administration (e.g. smoking prior to data collection) appears to have minimal effects on MMN amplitudes (Fisher et al., 2012; Inami et al., 2005; Inami et al., 2007). Upon arrival at the laboratory and following informed consent

procedures, participants completed the NART (Nelson, 1982; Nelson & Willison, 1991) before EEG electrodes were applied to scalp and face sites. Afterwards, participants were assessed with a neurophysiological battery of established MMN paradigms, during which they were instructed to view a silent, neutral video of their choosing and to ignore the presented auditory stimuli. Neutral videos were determined to be absent of humorous or aversive stimuli. Procedures were carried out following clearance by the relevant research ethics boards, including those of the Nova Scotia Healthy Authority, Saint Mary's University, and Mount Saint Vincent University.

2.2.5. Data analysis.

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk NY). Difference waves from each deviant type were analyzed separately, and then all deviants were analyzed together as a "combined" deviant. MMN amplitudes for each deviant were subjected to repeated-measures analysis of variance (ANOVA) procedures with a between-group (sex [male, female]) and two-within group factors (laterality [left, midline, right], and frontality [limited to the frontal (F) and central (C) regions]). Analysis of MMN latency was similar, but ANOVAs did not contain a site factor because MMN processes occur at the same time for all electrodes of interest. Planned pairwise comparisons were conducted to test interactions involving group. Additionally, we calculated effect size using Hedges' g (Hedges' $g = (M_2 - M_1) / SD_{pooled}$, where $SD_{pooled} = \sqrt{((SD_1^2 + SD_2^2) / 2)}$).

2.3. Results

2.3.1. MMN amplitude.

All MMN amplitudes at Fz were significantly different from zero. The amplitudes

(± SE) and 2-tailed one sample *t*-test statistics are summarized in Table 2. MMN amplitudes for each deviant type are discussed below. See Table 3 for mean (±SD) MMN amplitudes at Fz for all deviants.

Table 2

Mean amplitudes (± SE) at F_Z plus t*-statistic and significance values resulting from 2-tailed comparison of means against zero for all deviants of the optimal paradigm.*

	Mean amplitude (± SE)	*t*	Significance
Duration	-5.29 μV (0.36)	-14.46	$p < 0.001$
Gap	-3.49 μV (0.28)	-12.46	$p < 0.001$
Intensity	-3.26 μV (0.35)	-9.35	$p < 0.001$
Location	-1.56 μV (0.15)	-10.13	$p < 0.001$
Pitch	-3.72 μV (0.30)	-12.33	$p < 0.001$
Combined	-2.98 μV (0.21)	-13.96	$p < 0.001$

Table 3

Mean (± SD) MMN amplitudes (μV) at Fz for the five deviant types of the optimal paradigm, and a combination of all five deviants.

	Female	Male	*p*	Hedges' g
Duration	-5.76 (1.99)	-4.73 (2.16)	.12	0.50
Gap	-3.37 (1.68)	-3.64 (1.56)	.89	0.16
Intensity	-3.79 (2.12)	-2.63 (1.72)	.11	0.60
Location	-1.40 (1.04)	-1.75 (0.62)	.085	0.40
Pitch	-4.04 (1.87)	-3.32 (1.52)	.22	0.40
Combined	-3.12 (1.17)	-2.80 (1.30)	.70	0.26

2.3.1.1. *Duration deviant.*

Results showed a main effect of region, $F(1,31) = 14.04$, $p = .001$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. While there are no group x region x site interactions, $F(2,30) = 1.00$, $p = .38$, planned pairwise comparisons for the duration deviant revealed a trend for females (M = -4.99 μV, SD = 1.84) to have larger MMN amplitudes than males (M = -3.76 μV, SD = 1.57) at electrode C_3 ($p = .066$; Hedges' g = 0.66), and for females (M = -4.96 μV, SD = 1.96) to have larger MMN amplitudes than males (M = -3.76 μV, SD = 1.57) at electrode C_4 ($p = .066$; Hedges' g =

0.67). See Figure 2.

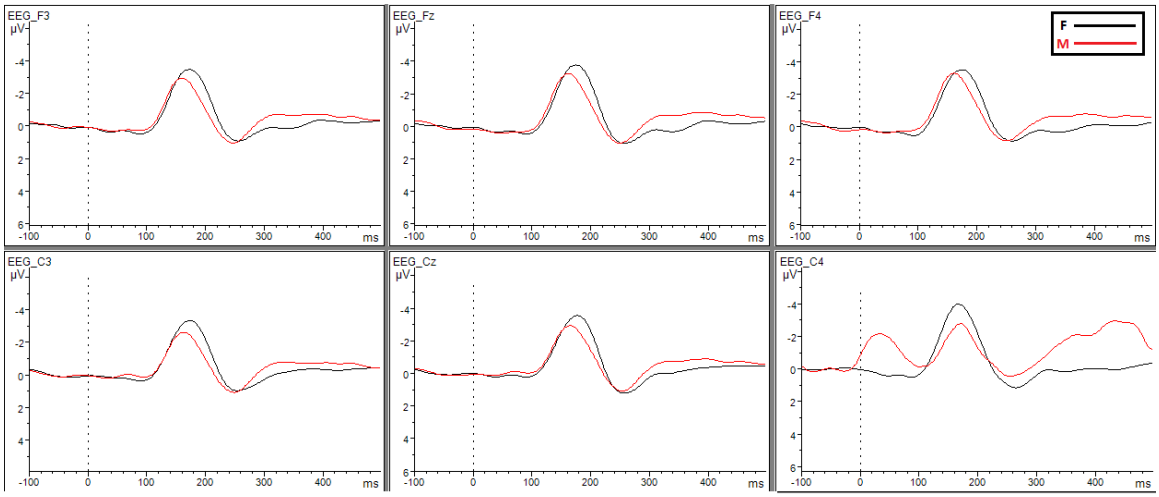

Fig 2. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the duration deviant. There was no significant difference between the groups at any sites ($p > .05$)

2.3.1.2. Gap deviant.

Results showed a main effect of region, $F(1,31) = 12.33$, $p = .001$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. There were no group x region x site interactions, $F(2,30) = 0.81$, $p = .46$. See Figure 3.

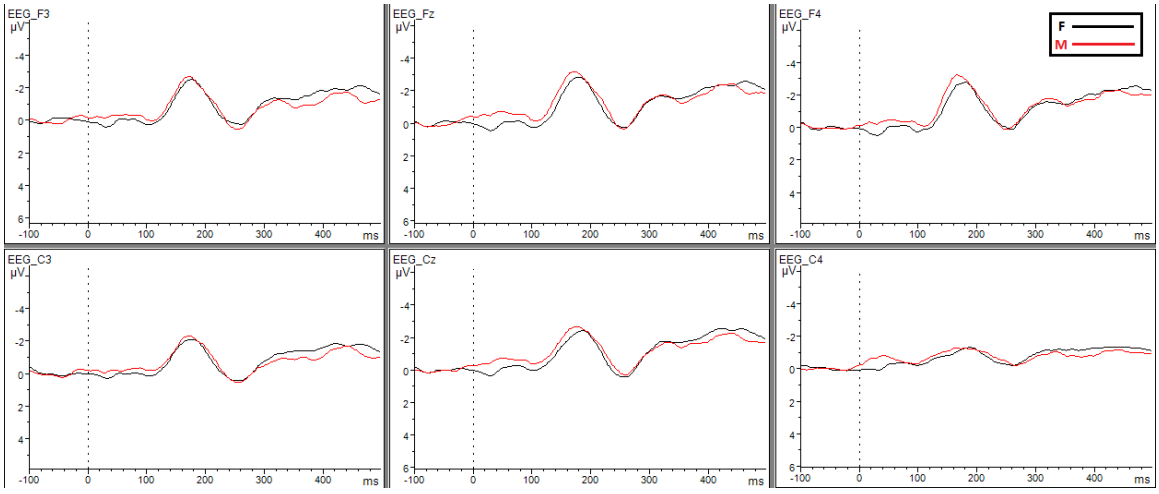

Fig 3. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) electrode sites for the gap deviant. There was no significant difference between the groups at any sites ($p > .05$).

2.3.1.3. *Intensity deviant.*

Results showed a main effect of region, $F(1,31) = 6.58$, $p = .015$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. While there are no

group x region x site interactions, $F(2,30) = 0.31$, $p = .74$, planned pairwise comparisons for the intensity deviant revealed a trend for females (M = -3.45 μV, SD = 1.85) to have larger MMN amplitudes compared to males (M = -2.63 μV, SD = 1.72) at electrode Cz ($p = .067$; Hedges' g = 0.66). See Figure 4.

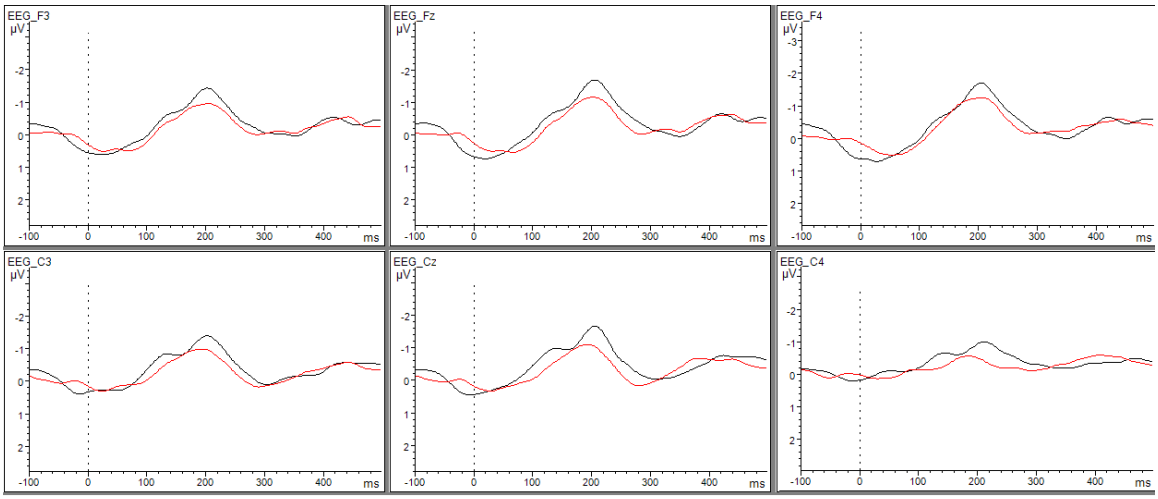

Fig 4. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the intensity deviant. There was no significant difference between the groups at any sites (p > .05).

2.3.1.4. *Location deviant.*

No significant group x region x site interactions, $F(2,30) = 1.05$, $p = .36$, however planned pairwise comparisons for the location deviant revealed MMN amplitudes to be significantly higher MMN amplitudes in males (M = -1.82 μV, SD = 0.93) compared to females (M = -1.06 μV, SD = 0.94), specifically at electrode F_3 ($p = .025$; Hedges' g = 0.81). The pairwise significant difference was followed up with an independent samples Mann Whitney U test, which also reported a significant sex difference at electrode F_3 (U = 69, $p = .016$). See Figure 5.

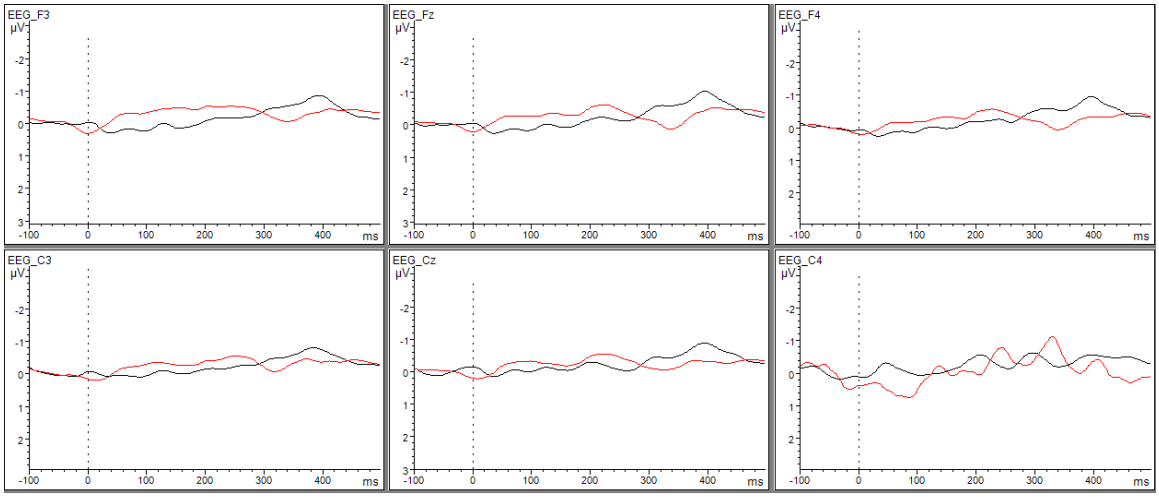

Fig 5. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) for the location deviant. There was a significant difference between groups at electrode site F_3 ($p < .05$).

2.3.1.5. *Pitch deviant.*

Results showed a main effect of region, $F(1,31) = 34.08$, $p < .001$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. While there are no group x region x site interactions, $F(2,30) = 0.74$, $p = .49$, planned pairwise comparisons for the pitch deviant revealed a trend for females (M = -3.46 μV, SD = 1.58) to have larger MMN amplitudes than males (M = -2.46 μV, SD = 1.36) at electrode C_4 ($p = .062$; Hedges' g = 0.68). The pairwise significant trend was followed up with an

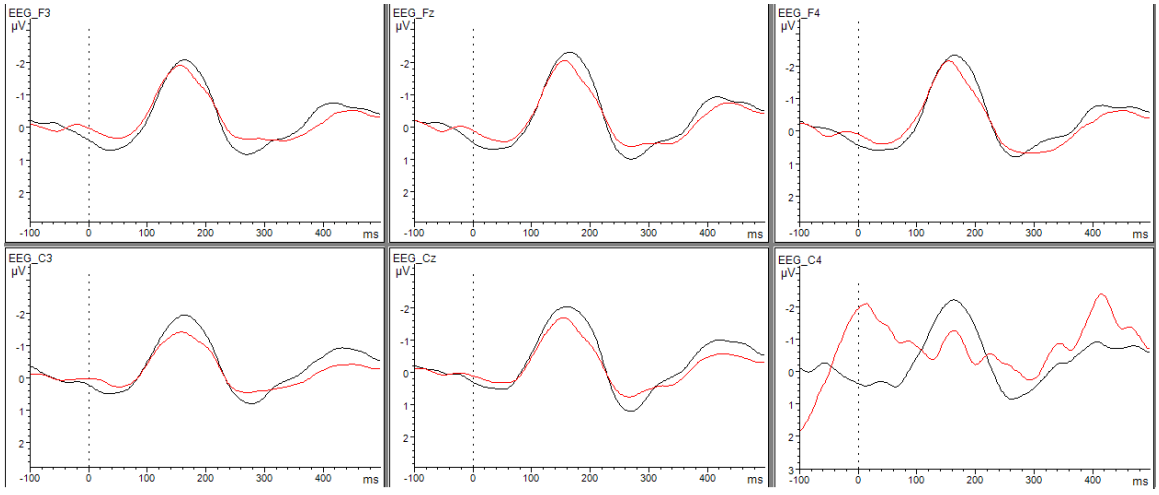

Fig 6. Grand averaged MMN difference waves for female (F) and male (M) participants frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the pitch deviant. There was no significant difference between the groups at any sites ($p > .05$).

independent samples Mann Whitney U test, which also reported a significant sex difference at electrode C_4 (U = 201, p = .016). See Figure 6.

2.3.1.6. *Combined optimal deviant.*

There were no main effects involving sex. There were no group x region x site interactions, $F(2,30) = 0.34$, p = .71. See Figure 7.

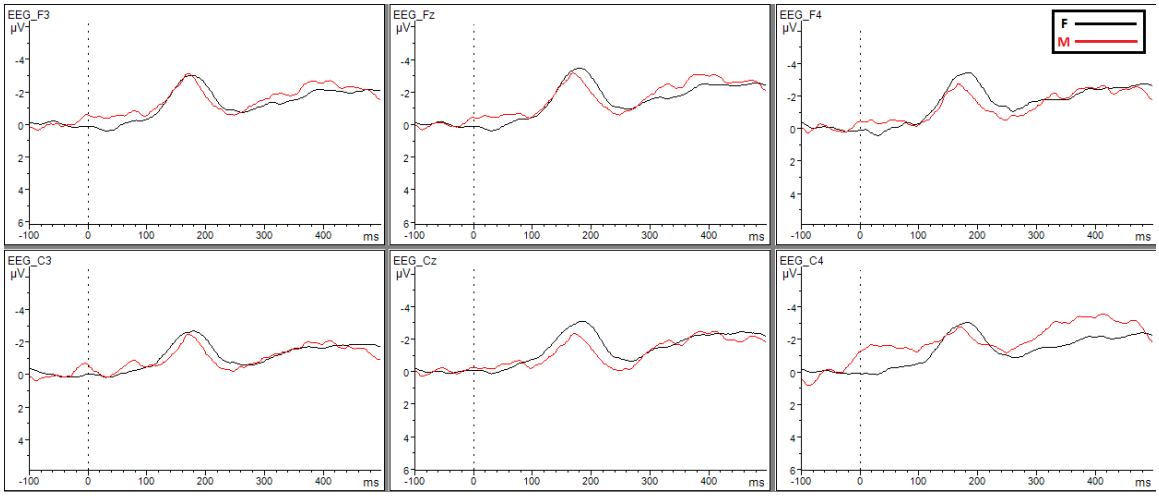

Fig 7. Grand averaged MMN difference waves for female (F) and male (M) participants frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the combined optimal deviant. There was no significant difference between the groups at any sites (p > .05).

2.3.2. MMN latency.

There was no significant difference between groups for MMN latency for any deviant type. See Table 4.

Table 4

Mean (± SD) MMN latency times (ms) for the five deviant types of the optimal paradigm and the combined optimal deviant.

	Female	Male	*p*	Hedges' g
Duration	167.56 (17.34)	163.60 (11.79)	.46	0.28
Gap	171.89 (18.81)	177.07 (18.90)	.44	0.27
Intensity	192.89 (36.37)	180.13 (33.86)	.31	0.36
Location	167.67 (41.30)	185.33 (46.68)	.26	0.40
Pitch	161.22 (20.55)	169.73 (23.88)	.28	0.38
Combined	176.33 (20.57)	173.07 (20.45)	.65	0.16

2.3.3. Correlations.

Participant age was positively correlated with duration MMN amplitudes (i.e. as

age increases, MMN decreases) at sites F_3 ($\rho = .40$, $p = .022$), F_4 ($\rho = .38$, $p = .032$), and Fz ($\rho = .38$, $p = .031$). See Figure 8.

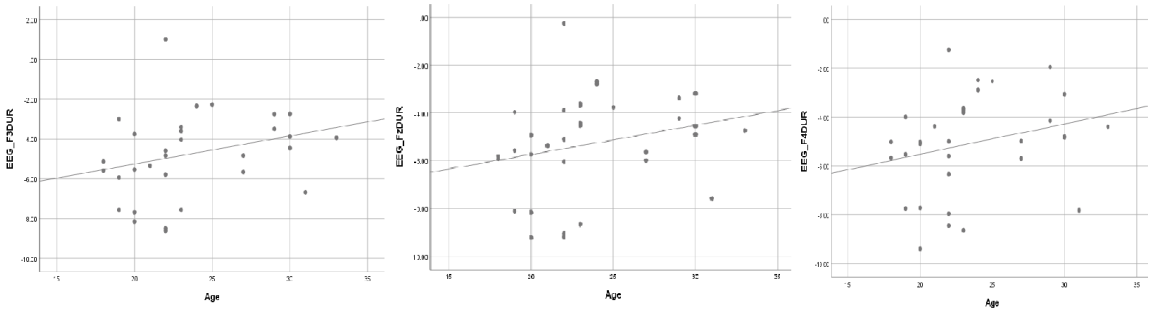

Figure 8. Scatterplots of correlations between duration MMN amplitudes and participant age at electrode sites F_3 (left), F_z (middle), and F_4 (right).

2.4. Discussion

It was hypothesized that we would not find a sex difference in MMN amplitudes in biological females compared to biological males using the "optimal" MMN paradigm. Overall, our results supported this hypothesis; the only statistically significant difference observed was that males were found to have enhanced MMN amplitudes compared to females when they were presented with the location deviant. One explanation for why we found the opposite effect with the location deviant could stem from an evolutionary perspective; when we think back to our ancestors, while females were often tasked with taking care of the home and children, it was males who were responsible for tasks outside of the home, such as hunting. Hunting requires many tracking skills, such as the ability to use sound localization to animal calls. Therefore, the fact that males were better at detecting an auditory change to a location deviant may be the result of an adaptive ability to detect changes in localization relative to females. Researchers have found evidence to support this theory using manual pointing tasks, verbal-response tasks, as well as assessing ERP patterns. In one study (Zündorf, Karnath, & Lewald, 2011), five

loudspeakers were arranged around the participants at 0°, 45°, and 90° angles while a target sound (one of five possible sounds including a cuckoo clock, laughter, a baby crying, a dog barking, or a telephone ringing) was presented from one of the five loudspeakers in a single-source condition and all five sounds were presented simultaneously in a multi-source condition. Participants operated a swivel-mounted hand pointer to indicate the location of the target sound in a manual pointing condition, or read out tag numbers (-90, -45, 0, 45, 90) in a verbal response task. Results indicated males were better at localizing the target sounds in a multi-source sound environment, and females were found to make more left-right errors in this condition (Zündorf et al., 2011). Another study (Lewald & Hausmann, 2013) replicated the study, but instead used an array of 91 loudspeakers ranging from -90° to 90° in a constant distance of 1.5 m from the participant. Participants were presented with one target and one distractor sound simultaneously and used the same swivel-mounted hand pointer to indicate the location of the target sound. Results found that females were more likely to experience the "pulling" effect (a bias to target localization toward that of the distractor sound), and males were found to have consistently better performance in target localization with the distractor sound (Lewald & Hausmann, 2013). An ERP study delivered an oddball sequence of pink noise bursts (50 ms, at 76 dB) by two loudspeakers to the left and the right of the participant (with a 60 cm distance from participant in each direction) while EEG data was recorded from 162 scalp sites. The results found males to be more accurate in detecting target sound locations and to have significantly higher P3 amplitudes compared to females during task performance (Simon-Dack, Friesen, & Teder-Sälejärvi, 2009). Similarly, in visual-spatial research, females were found to have a less developed

ability to localize a visual object than males when participants were asked to point to the location of a white or red light in a box, and females also made significantly more pointing errors than males (Sandström, 1953).

We found that participant's ages were positively correlated with MMN amplitudes in regards to the duration deviant. This means that as people get older, their ability to detect an auditory change in duration is lower, and this is consistent with previous research (Kiang, Braff, Sprock, & Light, 2009).

Although we only found one significant sex difference in only one of the deviant-types, the number of trends (accompanied by medium-to-large effect sizes) suggest that there may be biological differences in the way females and males process auditory change, as indexed by the MMN, although further research would need to be conducted. While the deviants used in this study are all pure tone deviants, it can be argued that the way we perceive duration, intensity, and pitch deviants can be related to the way we perceive these types of changes in language. Females are often regarded as superior in detecting language changes in both monolingual (Coates, 2016; Eckert, 1989; Eckert & McConnell-Ginet, 2003) and bilingual settings (Shin, 2013) with one author even arguing that women are an entire generation ahead of men in their ability to detect linguistic changes (Labov, 2001). Thus, it is not surprising that the trends we found showed females to be better at detecting an auditory change than males with these deviants. However, more research should be done in this area as the current study does not provide enough evidence to conclude an overall sex difference.

CHAPTER 3: MISMATCH NEGATIVITY IN FEMALES AND MALES AS MEASURED BY A COMPLEX PATTERN MMN PARADIGM (Experiment 2)

3.1. Introduction

It has been argued that MMN paradigms like the "optimal" MMN paradigm are not complex enough to elicit group differences when there is a subtle alteration in function between two groups (Rudolph et al., 2015). Some researchers have investigated traditional oddball MMN paradigms using a missing stimulus as a deviant (instead of the use of deviant tones differing in gap, intensity, duration, location, or pitch) and have been unable to elicit MMN unless the tones were played very rapidly (Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997). This, along with the problem demonstrated by Schröger (2001) that frequency deviants may contain an overlapping N100 enhancement, led researchers to investigate more complex forms of MMN paradigms that address these issues. Pattern paradigms are purported to probe higher order processes not engaged with the simple MMN paradigms, and can also easily record MMN data in one recording session.

One such pattern paradigm, the simple pattern MMN paradigm, was developed by Sculthorpe and Campbell (2011). With this paradigm, stimuli consisted of two pure tones (A and B) that were tested in two different conditions: an alternating pattern or an oddball sequence. In the pattern condition, the standard sequence consisted of an alternating pattern (e.g. ABABAB) while the deviant was a sequence where either the A or B tone repeated itself (e.g. ABABBA). In the oddball condition, the A tone served as the standard while the B tone served as the deviant (e.g. AAAABA). Results found that the MMN amplitudes were significantly more negative for the deviants in both conditions, however, the authors highlighted the possibility that the classic inverse relationship

between MMN amplitude and deviant probability is a consequence of N100 enhancement seen in previous research (Sculthorpe & Campbell, 2011).

A two-tone pattern paradigm may be too simple to observe subtle differences between groups; indeed, a recent study reported such a paradigm was only able to elicit differences between early phase psychosis patient and healthy controls later in illness progression, but not at first episode (Ells et al., 2018). A more complex pattern MMN paradigm was developed by Salisbury (2012) where the deviant is the absence of a sound rather than the presentation of a deviant one. An auditory task using one stimulus was presented in groups of six pure tones (50 ms duration, 330 ms stimulus onset asynchrony, 400 trials) with an intertrial interval of 650 ms while subjects watched a silent video; following Gestalt principles of proximity, the six tones were perceived as a single unit of sound. Occasionally, a deviant group would be presented with either a missing 4^{th} or missing 6^{th} tone, and both missing tones evoked a robust MMN (Salisbury, 2012). These results validated the use of this complex pattern MMN paradigm in a healthy control population. The complex pattern MMN paradigm has also been found to be sensitive enough to detect significant MMN deficits in highly sensitive populations like early-phase psychosis (Rudolph et al., 2015), something the simple two-tone pattern paradigm was not able to do (Ells et al., 2018).

These conclusions suggest that the complex pattern MMN paradigm may be more appropriate to investigate sex-based differences due to the relatively complex computation and comparison of auditory gestalt of grouping that may be more sensitive to subtle changes between groups. Based on previous research, it is hypothesized that

MMN amplitudes will be significantly larger in biological females when compared to biological males using the complex pattern MMN paradigm.

3.2. Methods

3.2.1. Participants.

Thirty-three participants (18 female, 14 male) self-reporting negative psychiatric, medical, neurological and alcohol/drug abuse histories, and non-use of medications were recruited from the general public. Participants were identical to those in Experiment 1, however data from one male was removed due to technical issues. Male and female participants were statistically equivalent to each other for age (p = .19) and NART scores (p = .22). See Table 5.

Table 5
Mean (± SD) age and NART scores for female and male participants (Experiment 2).

	Female	Male
Age	22.33 (6.80)	25.14 (4.56)
NART	34.94 (9.61)	39.00 (8.36)

3.2.2. Complex Pattern MMN paradigm.

Replicating Salisbury's (2012) and Rudolph's (2015) methodology, participants were presented with auditory patterns consisting of 500 standard patterns (six 1000 Hz 50ms tone pips in a row; p = .8) and one of two deviant patterns (missing 4th tone or

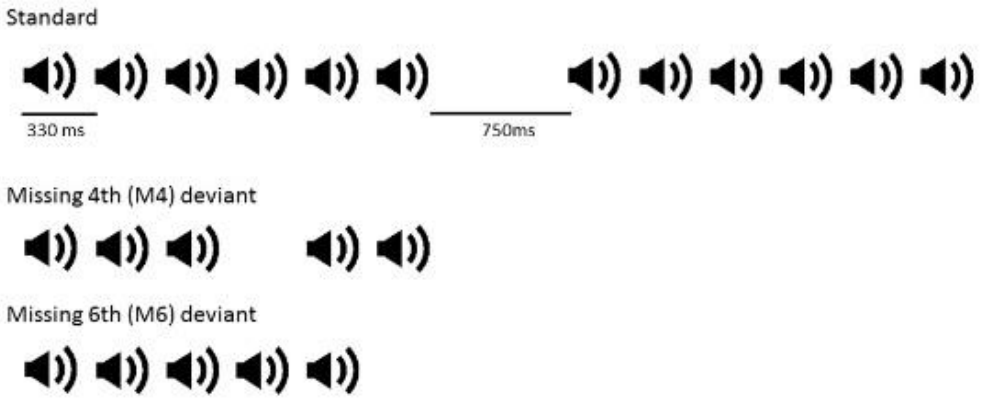

Fig 9. Schematic illustration of the complex pattern MMN paradigm (adapted from Salisbury, 2012)

missing 6th tone; $p = .1$ each). All stimuli were presented at an intensity of 75 dB SPL, with SOAs within patterns of 330ms and inter-pattern intervals of 750 ms. See Figure 9.

3.2.3. EEG recording and ERP computation.

EEG recording was identical to Experiment 1. Computation of MMN differed in that for the deviants, electrical epochs were time locked to the trigger emitted at the expected onset of the missing stimuli. Unlike typical MMN paradigms, no difference waves (e.g. deviant-minus-standard) were generated as the MMN was elicited by the absence of sound, negating the need for such a subtraction as there is no afferent activity from non-adapted sensory cells to account for.

3.2.4. Procedure.

Study procedures were identical to Experiment 1.

3.2.5. Data analysis.

Data analyses were identical to Experiment 1.

3.3. Results

3.3.1. MMN amplitude.

All MMN amplitudes at Fz were significantly different from zero. The amplitudes (± SE) and 2-tailed one sample *t*-test statistics are summarized in Table 6. There was no significant main or interaction effects found for MMN amplitudes elicited by either the missing 4th or missing 6th stimulus. See Table 7.

Table 6

Mean amplitudes (± SE) at F_Z plus t*-statistic and significance values resulting from 2-tailed comparison of means against zero for all deviants of the complex paradigm.*

	Mean amplitude (± SE)	*t*	Significance
Missing 4th	-2.26 (0.44)	-5.13	$p < .001$
Missing 6th	-1.53 (0.43)	-3.55	$p = .001$
Combined	-1.29 (0.32)	-4.00	$p < .001$

Table 7

Mean (± SD) MMN amplitudes (µV) at Fz for the two deviant types of the complex paradigm and the combined complex deviant.

	Female	Male	*p*	Hedges' g
Missing 4th	-1.86 (2.42)	-2.76 (2.57)	.72	0.36
Missing 6th	-1.18 (2.23)	-1.98 (2.71)	.69	0.33
Combined	-0.96 (1.86)	-1.72 (1.75)	.65	0.42

3.3.1.1. *Missing 4th deviant.*

Results showed a main effect of region, $F(1, 30) = 21.45$, $p < .001$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. There were no group x region x site interactions, $F(2,29) = 0.67$, $p = .52$. See Figure 10.

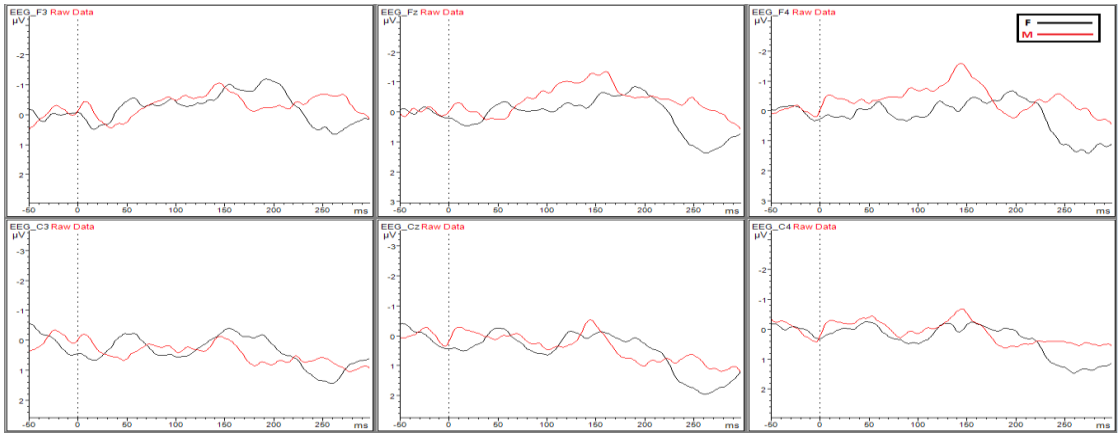

Fig 10. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the missing 4th deviant. There was no significant difference between the groups at any sites (p > .05).

3.3.1.2. *Missing 6th deviant.*

Results showed a main effect for region, $F(1,30) = 11.23$, $p = .002$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. There were no group x region x site interactions, $F(2,29) = 0.81$, $p = .46$. See Figure 11.

3.3.1.3. *Combined complex deviant.*

Results showed a main effect of region, $F(1,30) = 13.221$, $p = .001$, due to significantly larger MMN amplitudes at frontal (vs. central) sites. There were no group x region x site interactions, $F(2,29) = 1.12$, $p = .34$. See Figure 12.

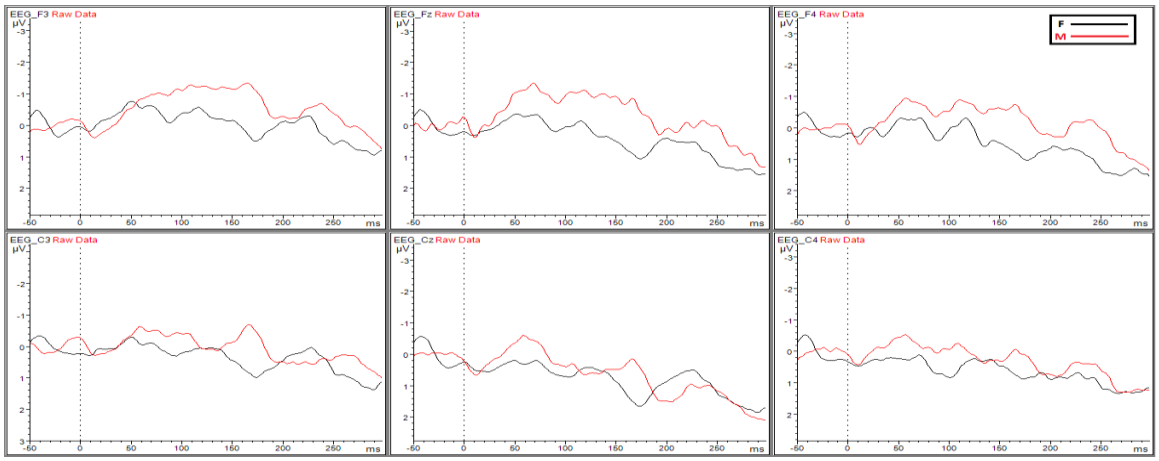

Fig 11. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the missing 6th deviant. There was no significant difference between the groups at any sites ($p > .05$).

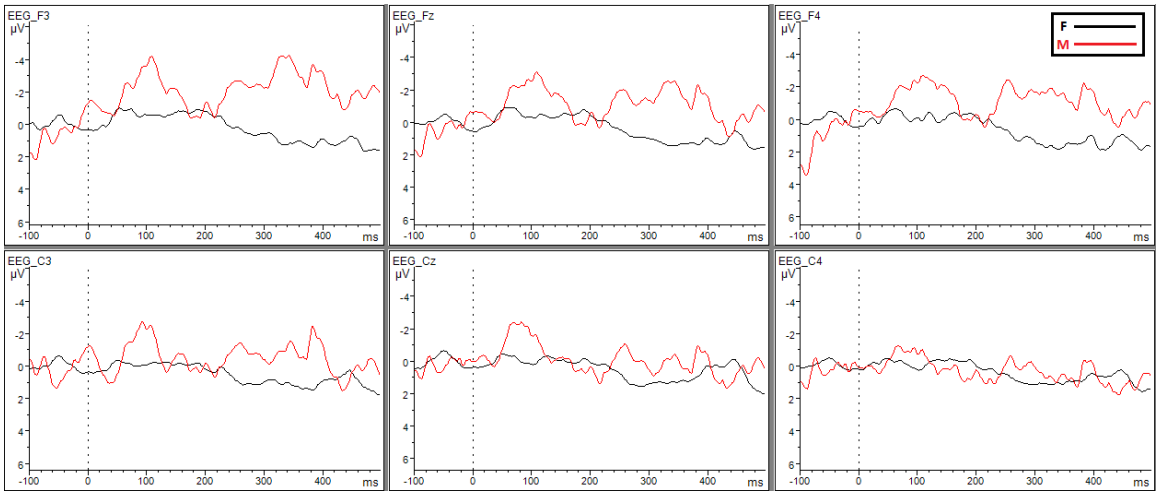

Fig 12. Grand averaged MMN difference waves for female (F) and male (M) participants at frontal (F_3, Fz, F_4) and central (C_3, Cz, C_4) electrode sites for the combined complex deviant. There was no significant difference between the groups at any sites ($p > .05$).

3.3.2. MMN latency.

There were no significant differences between groups for MMN latency for the missing 4th, missing 6th, or combined stimuli. See Table 8.

Table 8

Mean (± SD) MMN latency times (ms) for the two deviant types of the complex paradigm and the combined complex deviant.

	Female	Male	*p*	Hedges' g
Missing 4th	157.33 (30.59)	169.57 (34.22)	.30	0.38
Missing 6th	172.11 (50.54)	143.71 (35.19)	.071	0.64
Combined	166.78 (41.78)	158.86 (36.04)	.58	0.20

3.3.3. Correlations.

Participant age was negatively correlated with missing 6th MMN amplitudes (i.e. as age increases, MMN increases) at site F_3 (ρ = -.38, p = .030). See Figure 13.

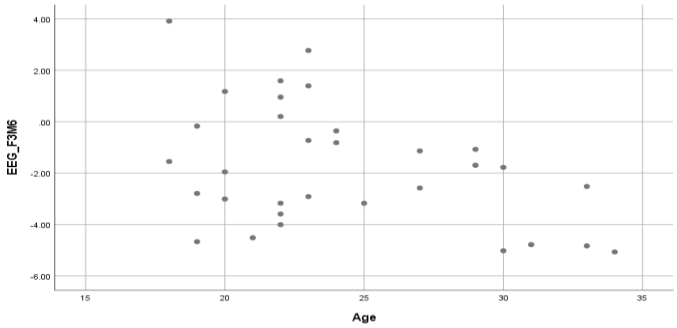

Figure 13. Scatterplot of correlation between missing 6th MMN amplitudes and participant age at electrode site F_3 (left).

3.4. Discussion

It was hypothesized that MMN amplitudes would be significantly enhanced in biological females when compared to biological males using the complex pattern MMN paradigm. Our results did not support this hypothesis and we found no significant sex differences for the missing 4th nor the missing 6th deviant. This could mean that the paradigm itself may not be appropriate to detect such sex differences. We had hypothesized that this paradigm could potentially be useful to detect sex differences as the complexity could be comparable to emotional MMN paradigms and it has been found to be sensitive enough to detect MMN deficits in highly sensitive clinical populations, but perhaps the sex differences in higher order brain processes are not robust enough to be detected as easily as MMN deficits in a declining population. Alternatively, it is possible that there are no biological sex differences in the way missing stimuli from a pattern are pre-attentively processed in the brains of healthy participants. In regards to clinical populations, sex differences in MMN have yet to be characterized (Riel, Lee, Fisher, & Tibbo, 2019); if the complex pattern paradigm is able to detect sex differences (as

exploratory analysis in our lab detected in early psychosis patients; Rudolph et al.'s 2015 data set, although not included in publication due to small sample sizes between biological sex groups), it would suggest that these differences are related to the disease, such as those seen in MDD (Qiao et al., 2015), and not due to biological sex differences at baseline. If in the future researchers are able to collect comparable size groups between sexes, it would be important to see if this paradigm is indeed able to detect biological sex differences in sensitive clinical populations, such as early phase psychosis and schizophrenia.

Participant ages were found to be negatively correlated with MMN amplitudes, meaning that as age increased, participants were found to actually be better able to detect auditory changes to the missing 6^{th} stimulus. This finding is interesting because it is opposite to what we found in Experiment 1. While Kiang and colleagues (2009) had found that MMN got progressively smaller as age increased, the most dramatic decline was found after age 40. There were only four participants in our data set that were over the age of 30, with the oldest being 34, so it is possible that our data set did not have a large enough age range to detect such an MMN decline. Although, this theory does not explain why we found MMN amplitudes to increase as age increased, nor does it explain why we found the correlation to be in the opposite direction in Experiment 1. One possibility is that the "optimal" paradigm used in experiment 1, much like the oddball paradigm used by Kiang and colleagues (2009), probes basic cognitive processes centred around auditory cortices that may decline more rapidly with age than higher order (i.e. prefrontal) processes probed by our complex pattern paradigm. The complexity of brain dynamics have been found to increase with age (Anokhin, Birbaumer, Lutzenberger,

Nikolaev, & Vogel, 1996) so it's possible that the higher order brain processes being probed by a missing stimulus deviant may actually improve as age increases, at least up to age 34, causing MMN amplitudes to increase as age increases in complex paradigms.

CHAPTER 4: GENERAL SUMMARY

It was our overall goal to determine if sex differences occur in central auditory processing, specifically in auditory change detection as indexed by MMN. We had hypothesized that we would find a significant sex difference: that MMN amplitudes will be significantly enhanced in biological females when compared to biological males, but only with the complex paradigm. The "optimal" multi-feature MMN paradigm, a paradigm with a better signal-to-noise ratio than the traditional two-tone oddball (Thönnessen et al., 2008), is thought to probe the more basic mechanisms associated with auditory change detection. It was thought that a complex pattern MMN paradigms, such as those proposed by Salisbury (2012), may be more appropriate to investigate sex-based differences due to the relatively complex computation and comparison of auditory gestalt of grouping that may be more sensitive to subtle changes. Overall, we report no sex differences with either the optimal MMN paradigm, or the complex pattern MMN paradigm. While trends for females to show larger MMN amplitudes were observed in response to the "optimal" MMN paradigm, the only statistically significant difference observed was that males were found to have enhanced location MMN amplitudes when compared to females. As this was only found at one site and for one deviant type, this suggests greater similarities than differences in auditory change detection of pure tones.

Within our two experiments, we found that as participant's age increased, they were found to be worse at detecting pure-tone deviants but better at detecting missing-tone deviants. While the basic cognitive mechanisms are found to decline with age (Kiang et al., 2009), higher order cognitive mechanisms have been found to improve with

age (Anokhin et al, 1996), and our results were able to provide support for these two theories.

The biggest limitation to our study was that we were not able to recruit equal numbers of biological males and females to compare sex differences. Power analyses conducted prior to testing determined at least eighteen participants were needed in each group, however we came up short in recruiting biological males; we only collected data for fifteen biological males in experiment 1, and fourteen biological males in experiment 2 due to one male's data having to be removed because of technical issues. Since we were underpowered, the probability of finding true significance is lessened. It is possible that with greater sample sizes we could be able to detect subtle sex differences that we were not able to identify in the current study. Though, it is important to note that all of our sex difference effect sizes (using Hedges' g) were always calculated to be in the moderate range. Thus, while we were unable to find statistical significance, this moderate effect size should encourage further investigations of sex differences as far as auditory change detection of pure tones goes.

Another limitation to this study was the decision to investigate sex differences without controlling for the female menstrual cycles. Females have often been excluded from research studies due to the complexity of controlling for menstrual cycles. Female hormone levels, such as estradiol, fluctuate greatly depending on the phase of the menstrual cycle, so females would have to be recruited and booked during a specific week of their cycle. It is often very difficult to differentiate where each phase begins and ends within a cycle, because without something to regulate the cycle (e.g. birth control pills) it is typically unique to each female. Using hormonal birth control adds another

complication as it causes alterations to the hormone levels of estradiol and progesterone. To our knowledge, no research has yet been done to investigate the influence that menstrual cycles may have on MMN. Without controlling for (and testing across) menstrual cycles, it would be difficult to conclude that a sex difference is or is not present.

Another possible future research direction would be to look at individuals who identify as transgender (particularly those who identify with the opposite gender of their assigned biological sex); we only included cis-gendered (a person who identifies with their assigned biological sex) individuals in this study but it would be very important to investigate the potential differential impact of sex and gender, how taking exogenous hormones (trans males on testosterone and trans females on estradiol) can affect biological sex differences in the brain, as well as MMN occurrence in non-binary gendered individuals.

In conclusion, this is the first study to our knowledge that investigated sex differences in a healthy population using a paradigm considered to be more complex than a two-tone oddball paradigm. We were not able to find enough evidence to conclude sex differences in MMN, suggesting that auditory change detection may be more characterized by sex similarities. In regards to clinical research, this study suggests that any observed sex differences in the MMN could be due to the illness itself (or the interaction of sex and illness) instead of biological sexual dimorphism.

References

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Santens, P., & De Letter, M. (2015). Sex differences in neurophysiological activation patterns during phonological input processing: an influencing factor for normative data. *Archives of Sexual Behaviour, 44,* 2207-2218.

Aleman, A., Kahn, R.S., & Selten, J.P. (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of General Psychiatry, 60,* 565-571.

Anokhin, A.P., Birbaumer, N., Lutzenberger, W., Nikolaev, A., & Vogel, F. (1996). Age increases brain complexity. *Electroencephalography and Clinical Neurophysiology, 99,* 63-68.

Arcia, E. & Conners, C.K. (1998). Gender differences in ADHD? *Journal of Developmental and Behavioral Pediatrics, 19*(2), 77-83.

Arnold, L.M. (2003). Gender differences in bipolar disorder. *Psychiatry and Clinics of North America, 26,* 595-620.

Asthana, H.S. & Mandal, M.K. (1998). Hemifacial asymmetry in emotion expression. *Behaviour Modification, 22,* 177-183.

Barnes, L.L., Wilson, R.S., Bienias, J.L., Schneider, J.A., Evans, D.A., & Bennett, D.A. (2005). Sex differences in clinical manifestations of Alzheimer Disease Pathology. *Archives of General Psychiatry, 62*(6), 685-691.

Bartley, E.J. & Fillingim, R.B. (2013). Sex differences in pain: a brief review of clinical and experimental findings. *British Journal of Anaesthesia, 111,* 52-58.

Beeson, P.B. (1994). Age and sex associations of 40 autoimmune disease. *Nature Immunology, 96,* 457-562.

Bergen, S.E., O'Dushlaine, C.T., Lee, P.H., Fanous, A.H., Ruderfer, D.M., Ripke, S., … & Corvin, A. (2014). Genetic modifiers and subtypes in schizophrenia: Investigations of age at onset, severity, sex and family history. *Schizophrenia Research, 154,* 48-53.

Bogetto, F., Venturello, S., Albert, U., Maina, G., & Ravizza, L. (1999). Gender-related clinical differences in obsessive-compulsive disorder. *European Psychiatry, 14,* 434-441.

Boutros, N., Zouridakis, G., Rustin, T., Peabody, C., & Warner, D. (1993). The P50 component of the auditory evoked potential and subtypes of schizophrenia, *Psychiatry Research, 47*(3), 243-254.

Breslau, N., Davis, G.C., Andreski, P., Peterson, E.L., & Schultz, L.T. (1997). Sex differences in posttraumatic stress disorder. *Archives of General Psychiatry, 54,* 1044-1048.

Cahill, L. (2006). Why sex matters for neuroscience. *Nature Reviews Neuroscience, 7,* 477-484.

Ceylan-Isik, A.F., McBride, S.M., & Ren, J. (2010). Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? *Life Sciences, 87,* 133-138.

Craig, A., Hancock, K., Tran, Y., Craig, M., & Peters, K. (2002). Epidemiology of stuttering in the community across the entire life span. *Journal of Speech, Language, and Hearing Research, 45,* 1097-1105.

Chiappa, K.H. (1990). *Evoked Potentials in Clinical Medicine.* New York: Raven Press.

Coates, J. (2016). *Women, Men and Language: A Sociolinguistic Account of Gender Differences in Language, Third Edition.* New York: Routledge Linguistics Classics.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L.B., Parvizi, J., & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience, 3*(10), 1049.

De Bellis, M.D., Keshavan, M.S., Beers, S.R., Hall, J., Frustaci, K., Masalehdan, A., … & Boring, A.M. (2001). Sex differences in brain maturation during childhood and adolescence. *Cerebral Cortex, 11*, 552-557.

Domes, G., Schulze, L., Böttger, M., Grossmann, A., Hauenstein, K., Wirtz, P.H., … & Herpertz, S.C. (2009). The neural correlates of sex differences in emotional reactivity and emotion regulation. *Human Brain Mapping, 31*(5), 758-769.

Eckert, P. (1989). The whole woman: Sex and gender differences in variation. *Language Variation and Change, 1*, 245-267.

Eckert, P. & McConnell-Ginet, S. (2003). *Language and Gender.* Cambridge: CUP.

Ells, E.M.L., Rudolph, E.D., Sculthrope-Petley, L., Abriel, S.C., Campbell, D.J., Tibbo, P.G., & Fisher, D.J. Alterations of a complex mismatch negativity (cMMN) elicited by a two-tone pattern paradigm in early-phase psychosis. *Biological Psychology, 135*, 128-135.

Fan, Y., Hsu, Y., & Cheng, Y. (2013). Sex matters: *n*-back modulated emotional mismatch negativity. *Cognitive Neuroscience and Neuropsychology, 24*(9), 457-463.

Feldman Barrett, L., Lane, R.D., Sechrest, L., & Schwartz, G.E. (2000). Sex differences in emotional awareness. *Personality and Social Psychology Bulletin, 26*(9), 1027-1035.

Filipek, P.A., Richelme, C., Kennedy, D.N., Caviness, V.S. Jr. (1994). The young adult human brain: an MRI-based morphometric analysis. *Cerebral Cortex, 4,* 344-360.

Fischer, A.H., Rodriguez Mosquera, P.M., van Vianen, A.E.M., & Manstead, A.S.R. (2004). Gender and culture differences in emotion. *Emotion, 4*(1), 87-94.

Fisher, D.J., Campbell, D.J., Abriel, S.C., Ells, E.M.L., Rudolph, E.D., & Tibbo, P.G. (2018). Auditory mismatch negativity and P300a elicited by the "Optimal" multi-feature paradigm in early schizophrenia. *Clinical EEG and Neuroscience, 49*(4), 238-247.

Fisher, D.J., Grant, B., Smith, D.M., Borracci, G., Labelle, A., & Knott, V.J. (2012). Nicotine and the hallucinating brain: effects on mismatch negativity (MMN) in schizophrenia. *Psychiatry Research, 196*, 181–187.

Fisher, D.J., Labelle, A., & Knott, V.J. (2008). The right profile: Mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. *Clinical Neurophysiology, 119*, 909-921.

Friedman, D. & Squires-Wheeler, E. (1994). Event-related potentials (ERPs) as indicators of risk for schizophrenia. *Schizophrenia Bulletin, 20,* 63-74.

Gaub, M. & Carlson, C.L. (1997). Gender differences in ADHD: a meta-analysis and critical review. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(8), 1036-1045.

Geary, D.C., Saults, S.J., Liu, F., & Hoard. M.K. (2000). Sex differences in spatial cognition, computational fluency, and arithmetical reasoning. *Journal of Experimental Child Psychology, 77,* 337-353.

George, M.S., Ketter, T.A., Parekh, P.I., Herscovitch, P., & Post, R.M. (1996). Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biological Psychiatry, 40,* 859-871.

Giedd, J.N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., & Rapoport, J.L. (1997). Sexual dimorphism of the developing human brain. *Progress in Neuro-Psychopharmacology & Bioloical Psychiatry, 21,* 1185-1201.

Giedd, J.N., Raznahan, A., Mills, K.L., & Lenroot, R.K. (2012). Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. *Biology of Sex Differences, 3,* 19-28.

Giedd, J.N., Shaw, P., Wallace, G., Gogtay, N., & Lenroot, R.K. (2006). *In Developmental Psychopathology. Volume 2. 2nd Edition.* John Wiley & Sons; Hoboken, N.J.

Goldstein, J.M. (2006). Sex, hormones and affective arousal circuitry dysfunction in schizophrenia. *Hormones and Behavior, 50,* 612-622.

Goldstein, J.M., Seidman, L.J., Horton, N.J., Makris, N., Kennedy, D.N., Caviness, V.S. Jr., … & Tsuang, M.T. (2011). Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cerebral Cortex, 11,* 490-497.

Gupta, A., Mayer, E.A., Fling, C., Labus, J.S., Naliboff, B.D., Hong, J., & Kilpatrick, L.A. (2017). Sex-based differences in brain alterations across chronic pain conditions. *Journal of Neuroscience Research, 95*(1-2), 604-616.

Gur, R.C., Richard, J., Calkins, M.E., Chiavacci, R., Hansen, J.A., Bilker, W.B., … & Gur, R.E. (2012). Age group and sex differences in performance on computerized neurocognitive battery in children age 8-21. *Neuropsychology, 26*(2), 251-265.

Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P., & Gur, R.E. (1999). Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *Journal of Neuroscience, 9*(10), 4065-4072.

Haaxma, C.A., Bloem, B.R., Borm, G.F., Oyen, W.J.G., Leenders, K.L., Eshuis, S., … Horstink, M.W.I.M. (2007). Gender differences in Parkinson's disease. *Neurology, Neurosurgery & Psychiatry, 78*(8), 819-824.

Halladay, A.K., Bishop, S., Constantino, J.N., Daniels, A.M., Koenig, K., Palmer, K., … & Szatmari, P. (2015). Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority. *Molecular Autism, 6*(36), 1-5.

Harasty, J., Double, K.L., Halliday, G.M., Kril, J.J., & McRitchie, D.A. (1997). Language-associated cortical regions are proportionally larger in the female brain. *Archives of Neurology, 54*(2), 171-176.

Harris, G.W. (1948). Neural control of the pituitary gland. *Physiological Reviews, 28*(2), 139-179.

Herlitz, A., Nilsson, L.-G. and Bäckman, L. (1997). Gender differences in episodic memory. *Memory & Cognition, 25*, 801–811.

Herting, M.M., Gautam, P., Spielberg, J.M., Kan, E., Dahl, R.E., & Sowell, E.R. (2015). The role of testosterone and estradiol in brain volume changes across adolescence: a longitudinal structural MRI study. *Human Brain Mapping, 35*(11), 5633-5645.

Hudson, J.I., Hiripi, E., Pope, H.G. Jr., & Kessler, R.C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 61,* 348-358.

Hung, A. & Cheng, Y. (2014). Sex differences in preattentive perception of emotional voices and acoustic attributes. *Cognitive Neuroscience and Neuropsychology, 25*(7), 464-469.

Hyde, J.S., & Linn, M.C. (1988). Gender differences in verbal ability: A meta-analysis. *Psychological Bulletin*, *104*, 53–69.

Inami, R., Kirino, E., Inoue, R., & Arai, H. (2005). Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity. *Pharmacology Biochemistry and Behavior, 80*, 453–461.

Inami, R., Kirino, E., Inoue, R., Suzuki, T., & Arai, H. (2007). Nicotine effects on mismatch negativity in nonsmoking schizophrenic patients. *Neuropsychobiology*, *56*, 64–72.

Jacobsen, T. & Schröger, E. (2001). Is there pre-attentive memory based comparison of pitch? *Psychophysiology, 38*(4), 723-727.

Jahshan, C., Cadenhead, K.S., Rissling, A.J., Kirihara, K., Braff, D.L., & Light, G.A. (2012). Automatic sensory information processing abnormalities across the illness course of schizophrenia. *Psychological Medicine, 42*(1), 85-97.

Joel, D. & Tarrasch, R. (2014). On the mis-presentation and misinterpretation of gender-related data: The case of Ingalhalikar's human connectome study. *PNAS, 111*(6), 637.

Kessler, R.C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders, 74,* 5-13.

Kiang, M., Braff. D.L., Sprock, J., & Light, G.A. (2009). The relationship between preattentive sensory processing deficits and age in schizophrenia patients. *Clinical Neurophysiology, 120*(11), 1949-1957.

Kimura, D. (2006). Human sex differences in cognition, fact, not predicament. *Sexualities, Evolution & Gender, 6*(1), 45-53.

Kring, A.M. & Gordon, A.H. (1998). Sex differences in emotion: Expression, experience, and physiology. *Journal of Personality and Social Psychology, 74*(3), 686-703.

Kujala, T., Lovio, R., Lepistö, T., Laasonen, M., Näätänen, R. (2006). The evaluation of multi-attribute auditory discimination in dyslexia with the mismatch negativity. *Clinical Neurophyiology, 117*(4), 885-893.

Labov, W. (2001). *Principles of linguistic change, vol. 2: Social factors.* Oxford: Blackwell.

Labrenz, F., Icenhour, A., Benson, S., & Elsenbruch, S. (2015). Contigency awareness shapes acquisition and extinvtion of emotional responses in a conditioning model of pain-related fear. *Frontiers in Behavioral Neuroscience, 9,* 318.

Lenroot, R.K., Gogtay, N., Greenstein, D.K., Wells, E.M., Wallace, G.L., Clasen, L.S., … & Giedd, J.N. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage, 36,* 1065-1073.

Lepistö, T., Kujala, T., Vanhala, R., Huotilainen, M., & Näätänen, R. (2005). The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Research, 1066(1-2),* 147-157.

Lewald, J. & Hausmann, M. (2013). Effects of sex and age on auditory spatial scene analysis. *Hearing Research, 299,* 46-52.

Lewin, C., Wolgers, G., & Herlitz, A. (2001). Sex differences favoring women in verbal but not in visuospatial episodic memory. *Neuropsychology*, *15*, 165–173.

Light, G.A., Swerdlow, N.R., Thomas, M.L., Valkins, M.E., Green, M.F., Greenwood, T.A., … & Turetsky, B.I. (2015). Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: Characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. *Schizophrenia Research, 163,* 63-72.

Linden, D.E.J. (2005). The P300: where in the brain is it produced and what does it tell us? *Neuroscientist, 11*(6), 563-576.

Loeber, R., Burke, J.D., Lahey, B.B., Winters, A., & Zera, M. (2000). Oppositional defiant and conduct disorder: a review of the past 10 years, part 1. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(12), 1468-1484.

Loyd, D.R. & Murphy, A.Z. (2014). The neuroanatomy of sexual dimorphism in opioid analgesia. *Experimental Neurology, 259,* 57-63.

Luders, E., Gaser, C., Narr, K.L., & Toga, A.W. (2009). Why sex matters: brain size independent differences in gray matter distributions between men and women. *The Journal of Neurosicence: The Official Journal of the Society for Neuroscience, 29,* 14265-14270.

McCarthy, M.M., Nugent, B.M., & Lenz, K.M. (2017). Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain. *Nature Reviews Neuroscience, 18*(8), 471-484.

McCombe, P.A. & Henderson, R.D. (2010). Effects of gender in amyotrophic lateral sclerosis. *Journal of General Medicine, 7,* 557-570.

McEwen, B.S. & Milner, T.A. (2017). Understanding the broad influence of sex hormones and sex differences in the brain. *Journal of Neuroscience Research, 95*(1-2), 24-39.

McLean, C.P., Asnaani, A., Litz, B.T., & Hofmann, S.G. (2011). Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatry Research, 45,* 1027-1035.

Näätänen, R. (1982). Processing negativity: An evoked-potential reflection. *Psychology Bulletin, 92*(3), 605-640.

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by the event-related potentials and other brain measures of cognitive function. *Behaviour and Brain Sciences, 13*(2), 201-233.

Näätänen, R. (2003). Mismatch negativity: clinical research and possible applications. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 48*(2), 179-188.

Näätänen, R., & Alho, K. (1997). Mismatch negativity--the measure for central sound representation accuracy. *Audiology & Neuro-otology, 2*(5), 341-353.

Näätänen, R., Kujala, T., Escera, C., Beldeweg, T., Kreegipuu, K., Carlson, S., & Ponton, C. (2012). The mismatch negativity (MMN) – a unique window to disturbed central auditory processing in ageing and different clinical conditions. *Clinical Neurophysiology, 123*(3), 424-458.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 118*(12), 2544-2590.

Näätänen, R., Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity (MMN): towards the optimal paradigm. *Clinical Neurophysiology, 115*(1), 140-144.

Nagy, E., Potts, G.F., & Loveland, K.A. (2003). Sex-related ERP differences in deviance detection. *International Journal of Psychophysiology, 48,* 285-292.

Nelson, H. E. (1982). *National Adult Reading Test (NART): For the assessment of premorbid intelligence in patients with dementia: Test manual*. Nfer-Nelson.

Nelson, H. E., & Willison, J. R. (1991). The revised national adult reading test–test manual. *Windsor, UK: NFER-Nelson*, *991*, 1-6.

Orton, S., Herrera, B.M., Yee, I.M., Valdar, W., Ramagopalan, S.V., Sadovnick, A.D., & Ebers, G.C. (2006). Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurology, 5,* 932-936.

Patel, S.H. & Azzam, P.N. (2005). Characterization of N200 and P300: selected studies of the event-related potential. *International Journal of Medical Science, 2*(4), 147-154.

Paus, T. (2010). Sex differences in the human brain: a developmental perspective. *Progress in Brain Research, 186,* 13-28.

Petersen, N., Kilpatrick, L.A., Goharzad, A., & Cahill, L. (2014). Oral contraceptive pill use and menstrual cycle phase are associated with altered resting state functional connectivity. *NeuroImage*, *90,* 24-32.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 118*(10), 2128-2148.

Potter, D., Summerfelt, A., Gold, J., & Buchanan, R.W. (2006). Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. *Schizophrenia Bulletin, 32*(4), 692-700.

Pritchard, W. (1968). Cognitive event-related potential correlates of schizophrenia. *Psychological Bulletin, 100,* 814-821.

Pritchard, W.S., Shappell, S.A., & Brandt, M.E. (1991). Psychophysiology of N200/N400: a review and classification scheme. *Advances in Psychophysiology, 4,* 43-106.

Qiao, Z., Yang, A., Qiu, X., Yang, X., Zhang, C., Zhu, X., … & Yang, Y. (2015). Gender effect on pre-attentive change detection in major depressive disorder patients revealed by auditory MMN. *Psychiatry Research: Neuroimaging, 234,* 7-14.

Raevuori, A., Keski-Rahkonen, A., & Hoek, H.W. (2014). A review of eating disorders in males. *Current Opinion Psychiatry, 27,* 426-430.

Regel, S., Meyer, L., Gunter, T.C. (2014). Distinguishing neurocognitive processes reflected by P600 effects: evidence from ERPs and neural oscillations. *Public Library of Science, 9*(5), e96840.

Reiss, A.L., Abrams, M.T., Singer, H.S., Ross, J.L., & Denckla, M.B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain, 119,* 1763-1774.

Riel, H., Lee, J.B., Fisher, D.J., & Tibbo, P.G. (2019). Sex differences in event-related potential (ERP) waveforms of primary psychotic disorders: A systematic review. *International Journal of Psychophysiology, in press,* https://doi.org/10.1016/j.ijpsycho.2019.02.006

Riva, D. & Giorgi, C. (2000). The cerebellum contributes to higher dunctions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain, 123*(5), 1051-1061.

Roth, W. (1977). Late event-related potentials and psychopathology. *Schizophrenia Bulletin, 3,* 105-120.

Rudolph, E.D., Ells, E.M.L., Campbell, D.J., Abriel, S.C., Tibbo, P.G., Salisbury, D.F., & Fisher, D.J. (2015). Finding the missing-stimulus mismatch negativity (MMN) in early psychosis: Altered MMN to violations of an auditory gestalt. *Schizophrenia Research, 166,* 158-163.

Rugg, M.D. & Coles, M.G.H. (Eds.). (1995). *Oxford psychology series, No. 25. Electrophysiology of mind: Event-related brain potentials and cognition.* New York, NY, US: Oxford University Press.

Salisbury, D.F. (2012). Finding the missing stimulus mismatch negativity (MMN): emitted MMN to violations of an auditory gestalt. *Psychophysiology, 49*(4), 544-548.

Sandström, C.I. (1953). Sex differences in localization and orientation. *Acta Psychologica, 9,* 82-96.

Salinas, J., Mills, E., Conrad, A., Koscik, T., Andreasen, N., & Nopoulos, P. (2012). Sex differences in parietal lobe structure and development. *Gender Medicine, 9,* 44-55.

Satterthwaite, T.D., Wolf, D.H., Roalf, D.R., Ruparel, K., Erus, G., Vandekar, S., … & Gur, R.C. (2015). Linked sex differences in cognition and functional connectivity in youth. *Cerebral Cortex, 25,* 2383-2394.

Schirmer, A., Escoffier, N., Li, Q.Y., Li, H., Strafford-Wilson, J., & Li, W. (2008). What grabs his attention but not hers? Estrogen correlated with neurophysiological measures of vocal change detection. *Psychoneuroendocrinology, 33*(6), 718-727.

Schröger, E. (2007). Mismatch negativity: A microphone into auditory memory. *Journal of Psychophysiology, 21*(3-4), 138-146.

Sculthorpe, L.D. & Campbell, K.B. (2011). Evidence that the mismatch negativity to pattern violations does not vary with deviant probability. *Clinical Neurophysiology, 122*(11), 2236-2245.

Shin, N.L. (2013). *Selected Proceedings of the 6th Workshop on Spanish Sociolinguistics.* Somerville, MA: Cascadilla Proceedings Project.

Simon-Dack, S.L., Friesen, C.K., & Teder-Sälejärvi, W.A. (2009). Sex differences in auditory processing in peripersonal space: an event-related potential study. *Neuroreport, 20*(2), 105-110.

Sorge, R.E., Mapplebeck, J.C.S., Rosen, S., Beggs, S., Taves, S., Alexander, J.K., … & Mogil, J.S. (2015). Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nature Neuroscience, 18*(8), 1081-1083.

Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., … & Toga, A.W. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral cortex, 17*(7), 1550-1560.

Sowell, E.R., Trauner, D.A., Gamst, A., & Jernigan, T.L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine & Child Neurology, 44,* 4-16.

Sur, S. & Sinha, V.K. (2009). Event-related potential: an overview. *Industrial Psychiatry Journal, 18*(1), 70-73.

Thönnessen, H., Zvyagintsev, M., Harke, K.C., Boers, F., Dammers, J., Norra, C., Mathiak, K. (2008). Optimized mismatch negativity paradigm reflects deficits in schizophrenia patients: A combined EEG and MEG study. *Biological Psychology, 77,* 205-216.

Tiemeier, H., Lenroot, R.K., Greenstein, D.K., Tran, L., Pierson, R., & Giedd, J.N. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. *Neuroimage, 49,* 63-70.

Trepat, E. & Ezpeleta, L. (2011). Sex differences in oppositional defiant disorder, *Psicothema, 23*(4), 666-671.

Tsolaki, A., Kosmidou, V., Hadjileontiadis, L., Kompatsiaris, I., & Tsolaki, M. (2015). Brain source localization of MMN, P300 and N400: Aging and gender differences. *Brain Research, 1603,* 32-49.

van der Stelt, O., & Belger, A. (2007). Application of electroencephalography to the study of cognitive and brain functions in schizophrenia. *Schizophrenia bulletin, 33*(4), 955-970.

Voyer, D., Voyer, S., & Bryden, M.P. (1995). Magnitude of sex differences in spatial abilities: Ameta-analysis and consideration of critical variables. *Psychological Bulletin, 117*, 250 –270.

Walder, D.J., Seidman, L.J., Cullen, N., Su, J., Tauang, M.T., & Goldstein, J.M. (2006). Sex differences in language dysfunction in schizophrenia. *The American Journal of Psychiatry, 163*(3), 470-477.

Winkler, I. & Czigler, I. (2012). Evidence from auditory and visual event-related potential (ERP) studies of deviance detection (MMN and vMMN) linking predictive coding theories and perceptual object representations. *International Journal of Psychophysiology, 83*(2), 132-143.

Witelson, S.F., Beresh, H., & Kigar, D.L. (2006). Intelligence and brain size in 100 postmortem brains: Sex, lateralization and age factors. *Brain, 129,* 386-398.

Yabe, H., Tervaniemi, M., Reinikainen, K., & Näätänen, R. (1997). Temporoal eindow of integration revealed by MMN to soun omission. *NeuroReport, 8,* 1971-1974.

Yang, X., Yu, Y., Chen, L., Sun, H., Qiao, Z., Qiu, X., … & Yang, Y. (2016). Gender differences in pre-attentive change detection for visual but not auditory stimuli. *Clinical Neurophysiology, 127*(1), 431-441.

Young, W.C., Goy, R.W., & Phoenix, C.H. (1964). Hormones and sexual behavior. *American Association for the Advancement of Science, 143*(3603), 212-218.

Zündorf, I.C., Karnath, H., Lewald, J. (2011). Male advantage in sound localization at cocktail parties. *Cortex, 47,* 741-749.

Appendix

National Adult Reading Test (NART; Nelson, 1982; Nelson & Willison, 1991)

National Adult Reading Test

Participant: _____ Date: _____

DEBT	SUBPOENA
DEBRIS	PLACEBO
AISLE	PROCREATE
REIGN	PSALM
DEPOT	BANAL
SIMILE	RAREFY
LINGERIE	GIST
RECIPE	CORPS
GOUGE	HORS D'OEUVRE
HEIR	SIEVE
SUBTLE	HIATUS
CATACOMB	GAUCHE
BOUQUET	ZEALOT
GAUGE	PARADIGM
COLONEL	FAÇADE

CELLIST
INDICT
DETENTE
IMPUGN
CAPON
RADIX
AEON
EPITOME
EQUIVOCAL
REIFY
INDICES
ASSIGNATE
TOPIARY
CAVEAT
SUPERFLUOUS
LEVIATHAN
PRELATE
QUADRUPED
SIDEREAL
ABSTEMIOUS
BEATIFY
GAOLED
DEMESNE
SYNCOPE
ENNUI
DRACHM
CIDEVANT
EPERGNE
VIVACE
TALIPES
SYNECDOCHE