An Investigation of the Auditory Mismatch Negativity Elicited by Complex Stimuli in Early-Phase Psychosis

by

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Abstract

Introduction: The ability to detect change in an otherwise standard auditory environment is indexed by the mismatch negativity (MMN), an event-related potential. Reduction of MMN has been well characterized in individuals with chronic schizophrenia, indicating deficits in basic sensory processing. However, there is a lack of MMN research in early-phase psychosis (EPP) with existing studies reporting conflicting results. This study aimed to investigate MMN elicited by more complex stimuli in EPP, hypothesizing that the complexity of MMN stimuli is better suited for identifying deficits in individuals with EPP whose cognitive functioning is more preserved. **Methods:** Thirteen EPP patients and 33 controls were included in the study, and demographic, symptom severity, and functional data were collected. MMN was measured with 1) a novelty paradigm which contained a standard and deviant tone in addition to a novel sound, and 2) an emotional paradigm containing neutral and angry spoken stimuli. **Results:** The two groups did not differ in MMN amplitude; however, we did observe shorter latency for the EPP group within the novelty paradigm, and correlations between MMN, negative symptoms, and overall functioning within the novelty paradigm in the EPP group. **Discussion:** Our hypothesis that EPP will exhibit reduced MMN amplitudes was not supported as we observed no between-group differences. Our results support the literature that good social and occupational functioning is associated with better sensory processing, and that shorter MMN latencies is associated with positive psychotic symptoms. Negative symptoms were also associated with neurocognitive deficits as measured by MMN.

List of Abbreviations and Symbols Used

BNSS	Brief Negative Symptom Scale
COMT	Catechol-O-methyltransferase
DISC1	Disrupted in schizophrenia 1
EEG	Electroencephalogram
EPP	Early-phase psychosis
ERP	Event-related potential
GABA	Gamma-aminobutyric acid
GTPase	Guanosine triphosphate enzymes
HC	Healthy control
IQ	Intelligence quotient
MMN	Mismatch negativity
NMDA	N-methyl-D-aspartate
NSEPP	Nova Scotia Early Psychosis Program
PANSS	Positive and Negative Syndrome Scale
PSYRATS	Psychotic Symptom Rating Scales
RGS4	Zinc finger protein 804A
SOFAS	Social and Occupational Functioning Assessment Scale
df	Degrees of freedom
etc	Et cetera
F	One-way repeated measures analysis of variance test
g	Hedges' g correlation coefficient
i.e.	In example

M	Mean
n	Sample size
p / Sig	Significance value
r	Spearman's row correlation coefficient
SD	Standard deviation
t	Independent samples t-test

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Chapter 1: Introduction

1.1 Psychosis and Schizophrenia: Historical Overview

Schizophrenia is a mental illness characterized by potentially chronic and severe disturbances in thought, perception, and behaviour. Onset occurs most often in young adulthood (i.e., ages 18 to 24), affecting males slightly greater than females (1.4:1) (McGrath, Saha, Chant, & Welham, 2008) and with an earlier age of onset in males. The incidence of schizophrenia has been reported at 15.2 per 100,000 persons in recent epidemiological studies (McGrath et al., 2008). The development and expression of schizophrenia symptoms is variable; while symptoms can be expressed abruptly, there is usually a gradual development (American Psychiatric Association, 2013). The core symptom clusters (Figure 1) of schizophrenia are classified into positive symptoms (i.e., hallucinations, delusions, thought disorder) which are symptoms in excess of or added to normal functioning; negative symptoms (i.e., anhedonia, asociality, blunted affect, avolition, alogia) which are deficits in normal mental functioning not usually seen within healthy individuals; and cognitive deficits (i.e., working memory, attention, processing speed). The loss of contact with reality that can occur due to these symptoms is referred to as psychosis and can create notable disturbances in significant areas of life such as work, relationships, and overall functioning.

A great portion of our current knowledge of schizophrenia is attributed to modern research techniques with valid and reliable measures. However, our understanding of the development of schizophrenia can be accredited to two historic psychiatrists: Emil Kraepelin and Eugen Bleuler.

Kraepelin approached mental illness with a view that a diagnosis should be based on the observation of patterns of symptoms over time rather than on any one pathognomonic symptom

or symptoms. From working with patients in a mental hospital, Kraepelin witnessed three manifestations of "insanity": disorganized and aimless behaviour (hebephrenia), lack of movement and agitated behaviour (catatonia), and delusions of grandeur (paranoia) (Beck, Rector, Stolar, & Grant, 2009). These types of "insanity" had an onset in early adulthood and the progression ultimately lead to an overall deteriorated condition (Warner, 2004). Patients with a combination of these symptoms, which we now know to be schizophrenia, were considered to have an illness called *dementia praecox*, implying a "dementia" that was associated with the deterioration of the mind. Kraepelin was very pessimistic regarding a patient's recovery of dementia praecox, and as his classification of the illness was adopted around the world, the concept that schizophrenia was a progressive and ultimately incurable illness was assumed (Warner, 2004).

Bleuler advanced Kraepelin's work of dementia praecox by characterizing the illness as a family of mental disorders (Healy, 2002). He argued that the illness could range from mild personality dysfunction to chronic dementia praecox, and the disturbances could be viewed in terms of symptoms that were necessary for diagnosis and those that did not need to be present for a diagnosis (Beck et al., 2009; Fuller, Schultz, & Andreasen, 2003; Moskowitz & Heim, 2011; Wing & Agrawal, 2003). Most notably, Bleuler proposed that a cognitive process whereby a splitting of psychic functioning occurred, often referred to as loosening of associations, was an essential feature of the illness. With this, he coined the term schizophrenia (i.e., schizo = to split; phrene = mind) (Ashok, Baugh, & Yeragani, 2012; Beck et al., 2009).

An additional scientist worth mentioning is John Hughlings Jackson. From his research, Jackson established a framework of disease that suggested "insanity" (referring to schizophrenia) was caused by a certain pathology localized in highly evolved (cortical) neurological centers of

the brain (Beck et al., 2009). Jackson also proposed that this "insanity" could be coded into two sets of symptoms, positive and negative. Positive symptoms are elaborations on what is normal and therefore propose an underlying deficit of a cognitive process, whereas negative symptoms are deficit states that imply disease-compromised brain structures (Beck et al., 2009). As initially mentioned, it is Jackson's framework of positive and negative symptomology that is still used today in identifying core symptom clusters of schizophrenia.

1.2 Prevalence and Costs of Schizophrenia

The lifetime prevalence of schizophrenia is estimated to be around 0.3-0.7% (American Psychiatric Association, 2013; Simeone, Ward, Rotella, Collins, & Windisch, 2015). Despite the low prevalence rate, its age of onset and potential chronicity results in health, social, and economic burden on patients, family members, friends, and supporters being high (Chong et al., 2016). The World Health Organization estimates that direct costs of schizophrenia in Western countries accounts for 7-12% of the gross national product (World Health Organization, 2001). In Canada, the direct healthcare and non-healthcare costs associated with schizophrenia are estimated to be over $2 billion per year, and when combined with deaths and unemployment attributed to the illness, the loss estimate is over $6 billion per year (Goeree et al., 2005). The burden of schizophrenia is increasing globally, and a lack of an effective treatment for schizophrenia will continue to critically impact individuals and families.

At any point in time, approximately 1% of the total population is diagnosed with schizophrenia, yet it remains to be one of the top 15 leading causes of disability (Global Burden of Disease, 2017). Individuals diagnosed with schizophrenia are more likely to be obese, have substance use problems, have hypertension, are at a higher risk of suicide, and have an increased

risk of premature mortality than the general population (Olfson, Gerhard, Huang, Crystal, & Stroup, 2015; Palmer, Pankratz, & Bostwick, 2005; Schoenbaum et al., 2017; Simon et al., 2018). Although the increased mortality rate is primarily due to the association with other health conditions (i.e., smoking, obesity, etc.), recent studies have shown that an increased risk of suicide appears to be most pertinent with newly diagnosed individuals, and delays in access to mental health care can further contribute to this increased suicide risk (Melle et al., 2006; Pompili et al., 2007; Ventriglio et al., 2016). To reduce this, protective factors for suicide in those with schizophrenia is important, and one such consistent factor is delivery and adherence to early and effective treatment (Hor & Taylor, 2010).

1.3 Prognosis and Outcomes of Schizophrenia

The prognosis of schizophrenia varies at the individual level as it depends on several factors such as access to health care, treatment adherence, familial support, and history of substance use. Studies have been consistent in finding that approximately 20-40% of individuals with schizophrenia experience remission or, at the very least, experience significant improvement, whereas approximately 25% of individuals find no meaningful improvement (Jääskeläinen et al., 2018; Manrique-Garcia et al., 2014; Menezes, Arenovich, & Zipurksy, 2006). It is not unusual for individuals to have relapses over the course of their illness; the most common cause of which appears to be treatment nonadherence (Emsley, Chiliza, Asmal, & Harvey, 2013).

Identification of specific predictors to foster a positive prognosis is crucial in aiding an individual with schizophrenia in establishing the best track to mental health possible. Factors associated with a positive outcome include not having a genetic predisposition, no substance

abuse issues, being of female sex, being married at the onset of the illness, having a late or acute onset, having a psychological stressor that preceded the onset, and having family involvement and support (Bromet, Naz, Fochtmann, Carlson, & Tanenberg-Karant, 2005; Emsley, Chiliza, & Schoeman, 2008; Harrison, Croudace, Mason, Glazebrook, & Medley, 1996; Jeppesen et al., 2008; Koskinen, Löhönen, Koponen, Isohanni, & Miettunen, 2010; Perkins, Gu, Boteva, & Lieberman, 2005).

Having good insight into one's illness is also clinically relevant in regard to prognosis as this will promote treatment-adherence, psychosocial functioning, and reduced hospitalization and utilization of emergency services (Shad, Keshavan, Tamminga, Cullum, & David, 2007). Additionally, an important point to consider regarding the prognosis of schizophrenia are the negative symptoms of the disorder (i.e., anhedonia, asociality, avolition, blunted affect, alogia). The positive symptoms usually respond well with medication, but the negative symptoms often remain persistent. Despite receiving treatment, 20-40% of individuals with schizophrenia exhibit persistent negative symptoms, which constitute a key element of the individual's overall suffering and significantly reduce their quality of life (Mäkinen, Miettunen, Isohanni, and Koponen, 2008). Therefore, treatment interventions, including pharmacology, that better manage negative symptoms is an ongoing area of research that is crucial to helping those with schizophrenia.

1.4 Etiology of Schizophrenia

The exact etiology of schizophrenia is unknown. However, it is clear that schizophrenia is a heterogenous illness (the exhibited symptoms involve a range of cognitive, behavioural, and

emotional dysfunctions that vary per individual) in which both genetic and environmental factors are involved.

A significant portion of the source of schizophrenia is attributed to genetics, which has a heritability of up to 81% (Sullivan, Kendler, & Neale, 2003). Research studies aiming to identify specific genes associated with the illness have found moderate to strong evidence in support of the COMT, DISC1, and RGS4 genes. The COMT gene is located in a fragment of chromosome 22q11, which when deleted, results in the psychiatric manifestations of schizophrenia and other psychoses (Williams, Owen, & O'Donovan, 2007). The DISC1 gene is involved in a wide range of cellular processes, including neurotransmitter signaling of dopamine (Dahoun, Trossbach, Brandon, Korth, & Howes, 2017). Dopamine has long been an area of interest in the etiology of schizophrenia as excess dopamine has been related to abnormalities in the mesolimbic and prefrontal brain regions, accounting for many of the positive symptoms seen in the illness (Brisch et al., 2014). The RGS4 gene modulates the activity of GTPase which is coupled with receptors involved in the signal transduction of dopamine, glutamate, and other neurotransmitters (Chen et al., 2004). Several studies have found an association with the RGS4 gene in individuals with schizophrenia, thereby positing that RGS4 is a candidate gene for the illness (Chen et al., 2004; Chowdari et al., 2002; Mirnics, Middleton, Stanwood, Lewis, & Levitt, 2001; Morris et al., 2004). More recently, however, a particular genome-wide association study identified a different gene involved in transcription regulation, ZNF804A, that far surpassed benchmark levels of significance testing for schizophrenia, suggesting that this locus is now one of the most compelling markers in schizophrenia genetic research to date (Chang, Xiao, & Li, 2017; Williams et al., 2011; Zhou et al., 2018). Nevertheless, concordance rates of schizophrenia in identical twins is about 50%, demonstrating that schizophrenia is not entirely a

genetic illness (Cardno et al., 1999).

Several environmental and obstetrical risk factors have also been associated with schizophrenia. Influenza infection in expectant mothers during the first trimester of pregnancy has been associated with schizophrenia in offspring (Brown et al., 2004), and elevated positive antibodies for chlamydia and herpes have been found more often in individuals with schizophrenia compared to healthy individuals (Gutierrez-Fernandez et al., 2015; Krause et al., 2010). Studies have also provided indirect support for a viral etiology. For example, household crowding and the likelihood of people being born in the winter or spring are increased among those with schizophrenia, which is consistent with a heightened exposure to viruses under these conditions (Pearce, 2001; Torrey & Yolken, 1998). Furthermore, perinatal and postnatal complications such as perinatal brain damage, delivery complications, low birth weight, prenatal exposure to infections, and prematurity have all been associated with schizophrenia (Cannon, Jones, & Murray, 2002; Kunugi, Nanko, & Murray, 2001). One of the most extensive studies examining obstetric complications in relation to schizophrenia found that individuals with schizophrenia were seven times more likely to have had perinatal brain damage and six times more likely to have been born preterm compared to controls (Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998).

All of the above have been considered potentially significant stressors on brain development, however in themselves do not explain in its entirety the development of schizophrenia in a heuristic model. The two-hit hypothesis provides an etiological theory of schizophrenia that allows for the interplay between genes and the environment. This hypothesis suggests that a prenatal or genetic "first hit" disrupts an aspect of brain development that places an individual at an increased risk of a "second hit", an environmental component, to occur later

in life thus potentially leading to schizophrenia (Bayer, Falkai, & Maier, 1999; Maynard, Sikich, Lieberman, & LaMantia, 2001). Although this etiological model of schizophrenia has been accepted among the research community, a recent meta-analysis conducted by Davis et al. (2016) submitted that a binary model, such as the two-hit hypothesis, may not be comprehensive enough to describe such a heterogenous illness that is schizophrenia. Rather, developing schizophrenia is influenced by more complex processes involving genetic risk combined with multiple interacting hits and vulnerability factors occurring at key periods of neurodevelopmental activity, which culminate in the expression of the disorder (Davis et al., 2016).

1.5 Early Intervention for Schizophrenia

In addition to our increased knowledge of schizophrenia and identifying factors associated with short-term and long-term outcomes, there is substantial evidence from service delivery and outcomes research to indicate that early identification and treatment can make a significant difference in the prognosis, symptom reduction, and overall quality of life for patients (Kuehn, 2010; Lambert, Karow, Leucht, Schimmelmann, & Naber, 2010; Larsen et al., 2011; Lieberman, Dixon, & Goldman, 2013; Perkins et al., 2005). Individuals who have a shorter duration of untreated psychosis respond better to treatment, and as such, their overall functioning is increased (Perkins et al., 2005). Furthermore, early treatment has been shown to demonstrate positive functional and clinical outcomes long-term (Larsen et al., 2011).

According to the World Health Organization (1998), the method and setting of early care and treatment are important factors in determining the outcome and prognosis for those with schizophrenia. Guidelines for implementing care for individuals with schizophrenia have been

developed and implemented in Europe, Australia, and New Zealand (Galletly et al., 2016; Hasan et al., 2012, 2013). The United States has yet to develop a standard of care for schizophrenia, conceivably due to inadequate financing of healthcare and lack of inclusive healthcare insurance policies (Liberman et al., 2013). However, in 2004 the American Psychiatric Association did develop a guideline for treating schizophrenia for practicing clinicians in the United States to help guide treatment protocols (Lehman et al., 2004). Additionally, in Canada, early intervention programs for those with schizophrenia are not governed by a national standard; instead, each program offers their own mandate and criteria regarding their intervention services. In 2016, Nolin, Malla, Tibbo, Norman, and Abdel-Baki (2016) conducted a cross-sectional study of Canadian early intervention services for schizophrenia to determine each clinic's evaluation of program quality, service organization, and content. Overall, essential components of care were similar across programs including easy access to services, early intervention, a range of evidence-based interventions, and delivery of thorough follow-up and continuing care (Nolin, Malla, Tibbo, Norman, & Abdel-Baki, 2016). Although Canadian early intervention services implement suitable service delivery for patients, health care is provincialized and so service delivery is subjected to regional priorities, resources, and financial limitations (Nolin et al., 2016).

1.6 Early-Phase Psychosis

As a result of research that has been conducted on schizophrenia over past decades, many researchers and clinicians now think of schizophrenia as a phased illness allowing for phase-specific treatments (Figure 2). For instance, the onset of psychosis may be preceded by months or years of psychological and behavioral abnormalities (i.e., disturbances in cognition, emotion,

perception, etc.), often referred to as the prodromal phase. The emerging development of these symptoms allows researchers and clinicians an opportunity to identify those at-risk for conversion to schizophrenia, thus providing a unique time for research on early treatment services (Larsen, Walker, & Compton, 2010). As such, programs (as mentioned in section 1.5) focusing on treatment for individuals who are within five years of their first psychotic episode, known as early-phase psychosis (EPP), have become more prominent worldwide. These programs not only focus on patient care but provide education and support regarding the importance of early treatment in schizophrenia.

For individuals with EPP, it is particularly important that treatment is obtained in order to have the greatest impact on outcomes, as studies have indicated that symptoms can significantly worsen after this critical period of time (Birchwood, Todd, & Jackson, 1998; Cahn et al., 2009; McGlashan & Johannessen, 1996), and cognitive functioning can continue to deteriorate following the onset of symptoms (Harvey et al., 1999; Kremen et al., 2010; Seidman, Buka, Goldstein, & Tsuang, 2006; Zanelli et al., 2019), although this concept has been challenged (Heaton et al., 2001). As previously mentioned, research has been consistent in showing that the duration of untreated psychosis has a negative effect on an individual's overall functioning and prognosis, so it makes sense that future directions of mental health focus on understanding EPP and identifying the illness as early as possible. A significant component of this research area is the effort made on identifying biomarkers for schizophrenia. Establishing a biomarker would help determine who needs treatment in order to help those in need as early as possible, while simultaneously avoiding unnecessary interventions for those who do not need treatment.

1.7 Biomarkers

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathogenic, or pharmacologic processes to a therapeutic intervention (Biomarkers Definitions Working Group, 2001). As schizophrenia is a heterogenous disorder, the severity of symptoms can predict important aspects of the illness, such as the degree of cognitive or neurobiological deficits (American Psychiatric Association, 2013), thus identifying a biomarker would be essential for improving diagnostic accuracy and treatment purposes.

To date, research on biomarkers in schizophrenia has looked at both molecular (i.e., DNA, RNA, proteins) and macroscopic (i.e., brain tissue) levels. However, no definitive biomarker has yet been established. In order for a biomarker to be successful, it must be reliably identified, available, and has to predict something of value, such as a diagnosis when there is uncertainty and individual treatment response (Weickert, Weikert, Pillai, & Buckley, 2013). It is likely that the heterogeneity of schizophrenia will need to be considered in the search for a biomarker, possibly resulting in several biomarkers that identify the multiple components underlying schizophrenia.

A prevalent area of interest in identifying potential biomarkers for schizophrenia is that of brain imaging and electrophysiological measures. These techniques can illuminate structural and functional connectivity abnormalities as well as chemical imbalances that are characteristic of schizophrenia. Electrophysiological measures may be particularly useful as they are relatively inexpensive and accessible, particularly compared to more sophisticated neuroimaging techniques. A particular electrophysiological measure of interest is event-related potentials (ERPs), which are derived from an electroencephalogram (EEG).

1.8 Event-Related Potentials

ERPs are small voltages generated in the brain in response to specific sensory, cognitive, or motor events/stimuli and reflect the summed activity of postsynaptic potentials created when a large number of neurons in nearby proximity fire together. The data obtained from an EEG contains the brain's response to a stimulus (the ERP) as well as noise, which is activity unrelated to the stimulus. The ERP is extracted by taking segments of data around a stimulus and then averaging together each trial thereby creating one averaged ERP waveform. The resulting ERP waveform can have a negative or positive deflection, which is related to its underlying neural component (i.e., the orientation of the polarity in the neural generators). The sequence of ERP peaks reflects the flow of information though the brain, and the voltage at each time point in a waveform represents the brains activity at that precise moment in time. When analyzing ERP data, both amplitude and latency are examined. Amplitude assesses the magnitude of a waveform and refers to when the voltage reaches a peak point. The magnitude of the maximum peak is thought to represent the relative amount of cortical resources allocated or the neural efficiency of the cognitive process being indexed (Light et al., 2010). Latency assesses the timing of the underlying neural component and is interpreted as a time interval between the onset of a stimulus and a cortical response. Latency is thought to inform us on how quickly the cognitive process being indexed takes place.

Modern use of ERP research began in 1964 with a cognitive study that revealed a negative ERP component which reflected a participant's preparation for an incoming stimulus (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The next major ERP study was undertaken in 1965 in which the P300 waveform was discovered; a component elicited in reponse to decision making (Sutton, Braren, Zubin, & John, 1965). Over the past several years,

research using ERP technolgy has continued to flourish; it is a noninvasive technique with high temporal resolution, that is, it can measure activity in milliseconds, allowing for specific and detailed information on cognitive processing. In individuals with schizophrenia, ERPs have been used to measure aspects of brain function that are impaired, thereby providing specific information about a patient's brain dysfunction. As previously mentioned, a core component of schizophrenia is neurocognitive dysfunction, and these deficits in attention, memory, processing speed, and critical thinking have been associated with poor functional outcomes (Niendam et al., 2006). Interestingly, studies have even found that cognitive deficits are present in individuals in the prodromal phase of schizophrenia (Häfner et al., 1992; Lencz et al., 2006). As neurocognitive deficits occur early on in the illness, it is possible that these deficits can predict conversion to schizophrenia, and ERP technology provides a great resource to study this possibility. ERP recordings are easily tolerated by most patients, which in a vulnerable population such as those with schizophrenia, is important. Many ERP related tasks are also passive in that they do not require the participant to be paying attention or give a behavioural response, which is also ideal in populations with known attention or motor deficits. Futhermore, ERPs have the potential to be useful biomarkers because they are related to neurotransmission, are relatively inexpensive, can be recorded portably, and are practical for large multisite studies (Light et al., 2015). Considering ERPs have been used in clinical practice to assess sensory responses (Harris, 1998), it is reasonable to expect that they could be adapted for the assessment of cognitive processing (Luck, 2011). Thus, cost and implementation are not major obstacles to the use of ERPs as biomarkers.

1.8.1 Simple vs. Complex Paradigms. The stimuli used in ERP paradigms can be viewed as simple or complex. Simple paradigms involve limited stimuli with few differing

attributes (i.e., duration, frequency, intensity) to allow for fundamental neural activity measures of well-defined computations (Langer et al., 2017). However, the use of simple paradigms often corresponds to artificial behavioural scenarios, so in order to measure neural activity during more ecologically valid behavioural scenarios that better relate to real-life, complex paradigms are used. These complex paradigms can include stimuli with several attributes, or variations on stimuli such as words, patterns, or environmental sounds (Langer et al., 2017). A common simple ERP paradigm is referred to as an "oddball paradigm", in which a standard stimulus and a deviant (oddball) stimulus are presented, and reactions to the deviant stimulus are recorded.

1.8.2 Mismatch Negativity. The ability to perceive a deviant sound in an otherwise standard auditory environment is referred to as auditory change detection. This basic sensory processing function reflects the brain's capacity to perform automatic comparisons of consecutive auditory stimuli and provides an index of sensory learning and perceptual accuracy (Garrido, Kilner, Stephan, Friston, & 2009). The change detection process is indexed by the mismatch negativity (MMN), an ERP occurring 100-250ms after the occurrence of an auditory deviant (Figure 3). MMN is most often measured by randomly inserting a sound that deviates in some way (e.g., frequency, duration, intensity, and/or location) from a repeated standard, or expected, sound (Näätänen, Paavilainen, Rinne, & Alho, 2007; Salisbury, 2012). The MMN waveform is the result obtained by subtracting the standard stimulus response from the deviant stimulus response. Since MMN can be elicited regardless of whether an individual is paying attention, it is considered to be a measure of preattentive processing (Näätänen et al., 2007). From an evolutionary standpoint, the ability to rapidly and automatically detect changes in an otherwise standard environment is an important adaptive trait that is essential for survival.

The neural generators of MMN are located bilaterally within the auditory cortex, specifically the anterior transverse temporal gyrus (Brodmann area 41) and the posterior transverse temporal gyrus (Brodmann area 42), which are also sometimes referred to as Heschl's gyri, and the superior temporal gyrus (Brodmann area 22), which is in the temporal lobe and part of the auditory cortex (see Figure 4). Neural activity in the frontal cortex also contributes to the MMN and is thought to be associated with involuntary switching of attention prompted by changes in the auditory environment (Giard, Perrin, Pernier, & Bouchet, 1990; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005). Thus, MMN has two main generators: the bilateral auditory cortex, which underlies preattentive auditory change detection, that likely then triggers the frontal cortex MMN generator, which is associated with the initiation of attention switching to the sound change (Näätänen & Kähkönen, 2009). The precise neural mechanisms behind the MMN generators are not yet established, but accumulating evidence advocates that a combination of both neural adaptation and hierarchical input is involved. For instance, auditory neural adaptation is the gradual decrease in response resulting from regular stimulation of an auditory stimulus. When a contrasting sound is presented, one that is different from what has been adapted to, a response is generated. However, this does not explain how MMN can be elicited by violations of abstract rules, such as interstimulus relationships or phoneme irregularity. Even a repeating sound in a random sequence of sounds can elicit MMN (Näätänen & Rinne 2002), implying that neural adaptation is not the only explanation for why MMN occurs. Furthermore, the fact that frontal generators are involved in MMN suggests an additional mechanism – a distribution of sources that overall contribute to auditory detection. As such, it is possible that MMN relies on a more complex architecture involving multiple interactions among hierarchical levels within the primary auditory cortex (Garrido et al., 2009).

It is thought that the auditory cortex creates an expectation of the auditory environment based on the repeated or standard sound, so that deviations elicit an error signal in the brain. Alterations of MMN can indicate both deficits in performing this specific change-detection process, as well as more general problems (i.e., central auditory function) with the brain's ability to process sounds, such as physiological deficits that allow for the discrimination and detection of sounds at the preattentional level thereby contributing to poor perception and neurocognitive functioning.

1.8.2.1 Mismatch Negativity and Schizophrenia. Dysfunction of basic sensory and cognitive information processing underlies schizophrenia (Javitt, 2009), and the MMN is the most robust and well documented neuroelectric marker of dysfunction observed in chronic schizophrenia (i.e., individuals who have had the illness for many years) (Umbricht & Krljes, 2005). Many studies have indicated that the MMN is consistently reduced in individuals with chronic schizophrenia compared to healthy controls, and interestingly, although psychosis can appear in other disorders, this deficit appears to be unique to schizophrenia (Baldeweg & Hirsch, 2015; Catts et al., 1995; Fisher, Labelle, & Knott, 2008; Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Light & Braff, 2005; Umbricht et al., 2003; Youn, Park, Kim, Kim, & Kwon, 2003). The overall reduction of the MMN amplitude in schizophrenia represents a deficit in basic sensory information processing.

MMN reduction in schizophrenia is not attributed to medication (Haigh, Coffman, & Salisbury, 2017; Michie, 2001), remains relatively stable during acute and non-acute phases of the illness (Shinozaki et al., 2002), and has been shown to be correlated with impaired daily functioning (Kawakubo & Kasai, 2006; Light & Braff, 2005a; Light & Braff, 2005b; Light et al., 2015; Rasser et al., 2011), positive symptoms (Fisher et al., 2008; Hirayasu et al., 1998; Oades,

Zerbin, Dittmann-Balcar, & Eggers, 1996), and negative symptoms (Fulham et al., 2014; Thiebes et al., 2017). MMN amplitude has also been found to decline with age in both schizophrenia patients and controls (Kiang, Braff, Sprock, & Light, 2009), though it is unclear if this is due to a decline in cognitive function, auditory function, or both.

The reduction of MMN in schizophrenia has been more consistent with certain types of deviant stimuli compared to others, and this appears to correlate with illness progression. For instance, pitch-deviant stimuli have found to be reduced in chronic schizophrenia but not for those in early phases of the illness; in contrast, intensity and duration-deviant stimuli are found to be more prominent within individuals in the early phases (Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Todd et al., 2008). In fact, duration-deviant MMN reduction has been one of the most consistent findings in both chronic schizophrenia and in early stages, possibly signifying a more pronounced duration-deficit in schizophrenia (Michie, 2001; Umbricht & Krljes, 2005). It is thought this pronounced deficit in duration MMN may arise as time-dependent processing reliant on a network of brain areas consisting of auditory cortex, areas of prefrontal cortex, and the basal ganglia (Michie et al., 2000). This suggests individuals with schizophrenia may have deficits in processing certain properties of auditory stimuli (i.e., stimulus duration) more so than other properties depending on the underlying neural network.

MMN could be used as a biomarker could be used to identify individuals at risk of developing schizophrenia or as a way of tracking illness progression. If MMN has the potential to identify at-risk individuals, then identifying abnormal (reduced) MMN waveforms early on in the course of the illness is necessary. On the other hand, MMN may be a better indicator of illness progression considering MMN deficits have not always been found in EPP but have been found to increase with duration of illness (Haigh, Coffman, & Salisbury, 2017). Seeing as the

type of deviant stimuli used may be effective at helping track the degenerative processes, more research focusing on the type of stimuli used in MMN paradigms is needed in order to fully assess this waveform's utility as a biomarker.

Reduced amplitudes of the MMN waveform have been related to progressive loss of grey matter volume in the left hemisphere of the brain, specifically the auditory cortex, which consists of the anterior transverse temporal gyrus and the superior transverse gyrus (Domján, Csifcsák, Drótos, Janka, & Szendi, 2012; Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007; Umbricht & Krljes, 2005; Vita, De Peri, Deste, & Sacchetti, 2012). Temporal gyrus gray matter volume reductions do not appear to be a result of illness duration or antipsychotic treatment, because studies have found this reduction already present in individuals at the time of their first psychotic episode (Hirayasu et al., 2000; Kasai et al., 2003; Sweet, Henteleff, Zhang, Sampson, & Lewis, 2009). Furthermore, and not surprisingly, the superior temporal cortices that contain these primary and secondary auditory cortices have been associated with auditory hallucinations in psychosis (Atagün et al., 2015; Dierks et al., 1999; Jardri, Pouchet, Pins, & Thomas, 2011; Kuhn & Gallinat, 2012; Modinos et al., 2013; Shinn, Baker, Cohen, & Ongur, 2013).

1.8.2.2 Mismatch Negativity and Glutamate. Glutamate is the primary excitatory neurotransmitter of the auditory system (Godfrey et al., 1997; Godfrey, Parli, Dunn, & Ross, 1988; Petralia & Wenthold, 2009). Neurotransmitters are chemical substances that cross a synapse and meditate nerve impulse transmission from one neuron to another. They excite or inhibit the post-synaptic neuron to enhance or reduce nerve impulse transmission as well as mediate long-term changes in the neuron such as maturation and learning (Petralia & Wenthold, 2009). In the auditory system, this results in accurate sound identification and localization, and the integration of sound with other sensory and motor responses (Petralia & Wenthold, 2009).

The rudimentary role of the auditory system is to identify both the localization and nature of a sound. This basic sensory function, auditory processing indicated by MMN, is deficient in schizophrenia and is thought to be linked to glutamatergic dysfunction. Antagonistic drugs (i.e., ketamine, phencyclidine) of glutamate receptors, particularly NMDA, have consistently been found to reproduce the symptoms of schizophrenia in healthy individuals (Cohen, Tsien, Goff, & Halassa, 2015; Javit, 2010; Javitt & Zukin, 1991; Krystal et al., 1994). Thus, a disruption of glutamatergic and circuitry may be a core underlying feature contributing to the symptoms of schizophrenia.

Interestingly, NMDA receptor antagonists have also been shown to attenuate MMN amplitudes to what is seen in those with schizophrenia (Javitt, Steinschneider, Schroeder, Arezo, 1996; Umbricht et al., 2000), suggesting an overall connection between MMN, glutamate, and schizophrenia. Further contributing to this, post-mortem studies of individuals with schizophrenia indicate that the degeneration of brain volume primarily involves a reduction of dendrites (Feinberg, 1983; McGlashan & Hoffman, 2000; Moyer, Shelton, & Sweet, 2015), and a candidate mechanism for this reduction includes glutamatergic excitotoxicity, that is, where nerve cells are damaged by excessive stimulation of glutamate (Coyle, 1996; McCarley, Hsiao, Freedman, Pfefferbaum, & Donchin, 1996; Monnerie, Shashidhara, & Le Roux, 2003; Olney & Farber, 1995; Salisbury et al., 2007). Thus, the relationship between MMN, NMDA, and dendrite physiology may be particularly important for understanding the brain abnormalities of schizophrenia (Salisbury et al., 2007).

1.8.2.3 Mismatch Negativity in Early-Phase Psychosis. In a meta-analysis conducted by Erickson, Ruffle, and Gold (2016), it was found that MMN deficits may not develop in a linear manner, but that MMN impairment worsens during the early stages of schizophrenia (i.e., EPP)

and then stabilizes after this critical period has passed. Although the reduction of MMN in chronic schizophrenia has been a consistent finding, it has been less so for individuals with EPP (Fisher et al., 2018; Hay et al., 2015; Magno et al., 2008; Perez et al., 2014; Rudolph et al., 2015; Salisbury et al., 2007). This inconsistency might be in part explained by the methodology used, as simpler MMN paradigms, while eliciting differences in chronic schizophrenia, may not be complex enough for deficits to be observed in younger more cognitively preserved EPP participants (Salisbury, 2012). Erickson et al. (2016) also suggested that MMN impairment is ultimately a consequence of higher-order auditory expectancy deficits, a statement that coincides with this notion.

In light of this, studies implementing more complex paradigms and/or utilizing more complex stimuli in EPP have been conducted. In our lab, Fisher et al. (2019) compared EPP and chronic schizophrenia patients in a complex stimuli MMN paradigm elicited by phonemes in which they found significant MMN reductions within the chronic schizophrenia group relative to controls, but not the EPP group. Ells et al. (2018) also examined the use of a complex two-tone MMN paradigm in EPP to see if using a complex paradigm would be more appropriate; they observed no group differences, but did note that the MMN amplitude was consistently more reduced in patients who had a longer duration of illness, and as such, complex paradigms may be useful in indexing neurocognitive deficits in later stages of the illness, but not at the early phase (Ells et al., 2018). In contrast to the results of these studies, Rudolph et al. (2015) used an abstract missing stimulus paradigm (in which a fourth or sixth stimulus was missing) requiring complex cortical computations and found that MMN amplitudes elicited by missing stimuli did indeed reveal amplitude reductions in EPP patients, demonstrating that deficits can be identified by using this paradigm early in the illness (Rudolph et al., 2015). Overall, the evidence to

support the notion that paradigms with complex stimuli may better eludciate MMN deficits in EPP whose cognitive functioning is more preserved, is inconsistent and not entirely understood, and therefore more studies are required.

1.8.2.4 Mismatch Negativity and Biological Sex. Biological sex is a component that is often overlooked in neurophysiological research of schizophrenia (Riel, Lee, Fisher, & Tibbo, 2019). This is concerning considering sex differences exist in areas that are crucial to the understanding and management of the illness, such as diagnosis, treatment, and prognosis. For instance, males have an earlier onset of psychosis, exhibit more negative symptoms and cognitive deficits, are at a greater risk of developing schizophrenia, and are reported to demonstrate more neural structural changes than females (Abel, Drake & Goldstein, 2010; Aleman, Kahn, & Selten, 2003; Leung & Chue, 2000; Nopoulos, Flaum, & Andreasen, 1997). There is also evidence recommending sex-specific treatment for schizophrenia, as the experience of psychosis, and response to antipsychotic medication, can differ for males and females (Goldstein, 1997; Goldstein & Link, 1988; Howard et al., 2001; Morgan, Castle, & Jablensky, 2008).

Within MMN research of healthy individuals, reports of sex differences have been limited and inconsistent; one study found a greater amplitude reduction in males than females (Barrett & Fulfs, 1998), another found no difference in amplitude but that females had longer latencies than males (Aaltonen, Eerola, Lang, Uusipaikka, & Tuomainen, 1994) while another found no sex differences at all (Kasai et al., 2002). In participants with schizophrenia, the examination of sex on MMN has also been scarce with conflicting results similar to that of controls (Champagne, Mendrek, Germain, Hot, & Lavoie, 2014; Hiraysau et al., 1998, Light et al., 2015). Thus, our understanding of role sex has on MMN is unclear, which is substandard

because if differences are present within healthy individuals then the underlying pathology of schizophrenia may affect males and females differently as well. If we are to gain a comprehensive understanding of MMN as a potential biomarker for schizophrenia, then all aspects of MMN must be considered, and this includes the study of sex differences.

1.9 Paradigms and Hypotheses

The idea that MMN has the potential to be a biomarker for schizophrenia is a compelling reason to conduct more comprehensive research on MMN in EPP. The inconsistent findings of reduced MMN in EPP demonstrates that more reliable studies need to be conducted, and studies using more complex stimuli, to potentially better clarify MMN, are needed. Thus, to address deficits in the current EPP MMN literature, and to introduce unique complex-based stimuli paradigms as a measurement for MMN, we implemented two paradigms, both of which have not yet been employed in an EPP population.

The first paradigm we implemented is unique in that, unlike the traditional oddball paradigm which consists of a standard and deviant stimulus, this novelty paradigm consists of a standard, deviant, and novel stimulus that is a complex sound representative of the 'real world' environment (i.e., baby cry, sneeze, honking horn). This paradigm was implemented in individuals with schizophrenia when Fisher et al. (2014) examined MMN in hallucinating patients and MMN during an acute psychotic episode – a time in which symptoms of psychosis are likely to be most severe. Their results indicated that patients had reduced MMN amplitudes compared to controls, and these were correlated with auditory hallucinations; as such, the presence of auditory hallucinations may contribute to the sensory and cognitive information processing deficits found in schizophrenia (Fisher et al., 2014). The objective of using the

novelty paradigm in this study was to introduce ecologically valid complex stimuli to individuals with EPP, a population that is more cognitively preserved than chronic schizophrenia.

The second MMN paradigm we implemented was an emotional paradigm initially developed by Schirmer, Striano, and Friederici (2005) in which they examined sex differences of vocal emotional processing and vocal change detection in healthy participants using a paradigm that consisted of emotional (angry and happy) and neutral stimuli. They found that females, not males, exhibited larger MMN amplitudes to emotional stimuli and emotional vocal change, suggesting that even though both sexes detect change in voice preattentively, only females recruit additional processing resources when the change in voice is emotional (Schirmer, Simpson, & Escoffier, 2007; Schirmer, Striano, & Friederici, 2005). A similar result was found in a more recent study (Hung & Cheng, 2014) in which healthy individuals were presented with an emotional paradigm with sounds elicited by male and female speakers in angry, happy, and neutral intonations. The authors found that, irrespective of the sex of the presented voice, female participants displayed larger MMN amplitudes in response to fearful stimuli than male participants (Hung & Cheng, 2014).

In light of Schirmer's results, her lab investigated the role estrogen may have in the detection of vocal emotional processing. They found that participants with higher levels of estrogen had smaller MMN amplitudes to neutral stimuli compared to individuals with low levels of estrogen, and that this effect occurred in both males and females (Schirmer et al., 2008). However, because females have higher estrogen levels on average than males, females may be less sensitive to neutral change and as a result their threshold for attention may be higher than males (Schirmer et al., 2008). In an exploratory analysis of MMN elicited by this paradigm, we aimed to expand on research examining sex differences in ERP methodology, a component that

is often understudied, and determine whether these sex differences exist among individuals with EPP.

In sum, reduction in MMN has been characteristic of those with chronic schizophrenia, but not in those with EPP. This inconsistency may be due to the type of stimuli used, as the stimuli in previous paradigms was too simple to elicit MMN in EPP whose cognitive functioning is more preserved. Thus, the goal of this research was to investigate MMN in EPP elicited by more complex stimuli. As an exploratory analysis, we also examined whether the MMN response is moderated by biological sex. This will be the first study to implement an emotional and novelty paradigm in an EPP population and thus be particularly unique in the literature. Conducting this research will have clinical implications by further supporting or opposing the use of MMN as biomarker for schizophrenia, as well as implications for neurological research by illuminating auditory deficits in EPP.

Based on the findings of previous research, we hypothesized that 1) the EPP group would exhibit reduced MMN amplitudes relative to their healthy control counterparts, and that 2) females in both the EPP and control group would exhibit larger MMN amplitudes in response to the emotional stimuli and vocal change, compared to males, in the emotional paradigm.

Chapter 2: Methodology

2.1 Participants

Individuals aged 18 to 35 inclusive diagnosed with EPP were recruited from the Nova Scotia Early Psychosis Program (NSEPP). The NSEPP is the largest early intervention program in Atlantic Canada, focusing on early intervention services for those in the first five years of a psychotic illness. In addition to being the age range at the NSEPP, this age sample had also been selected as MMN has been shown to steeply degrade past age 40 (Kiang, Braff, Sprock, & Light, 2009). Patients who previously agreed to be approached for research studies were contacted to determine interest; for those interested in participating, the screening process was performed by H.R. Healthy controls, also aged 18 to 35, were recruited from the community through online advertisement and word-of-mouth.

2.2 Inclusion and Exclusion Criteria

Participants were excluded if they met the following criteria: history of a head injury resulting in a loss of consciousness; diagnosis of epilepsy or any other neurological disorder; received electroconvulsive therapy within the past year; experience of extrapyramidal symptoms which could affect ERP recordings; or an abnormal audiometric assessment. Additionally, EPP participants were excluded if they had a current co-morbid diagnosis of a psychiatric illness, including current substance use disorder based on the DSM-5 as assessed by their treating psychiatrist. Patients whose clinicians diagnosed or had a working diagnosis of schizophrenia were included due to the specificity of MMN deficits to schizophrenia. HCs were excluded if they were currently diagnosed with, or had a history of any psychiatric illness, or in the process of seeing a psychiatrist for a possible diagnosis.

2.3 Measures

Ratings on clinical scales were recorded for each EPP patient and included the Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Lindenmayer, 1989), the Psychotic Symptom Rating Scales (PSYRATS; Haddock, McCarron, Tarrier, & Faragher, 1999), the Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011), and the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman, Skodol, & Lave, 1992). To quantify an approximate premorbid IQ, both groups completed the National Adult Reading Test (NART; Bright, Jaldow, & Kopelman, 2002).

The PANSS is a measure of symptom severity of positive and negative symptoms, as well as general psychopathology, in individuals with schizophrenia. Patients are rated on a scale of 1 to 7 (1 = not present; 7 = extremely severe) on their symptomology by a trained interviewer with higher scores indicating worse symptoms. The PSYRATS was implemented as a measure of the presence or absence and severity of auditory hallucinations. Of the 11 symptoms, each is rated on a 4-point scale (0 = not present/rare; 4 = extremely severe) by a trained interviewer with higher scores signifying worse symptoms. The BNSS measures the severity of negative symptoms (anhedonia, asociality, avolition, blunted affect, alogia) and distress. Each symptom is rated on 6-point scale (0 = normal; 6 = severely impaired) by a trained interviewer with higher scores representing worse symptoms. The SOFAS is a measure of social and occupational functioning that is not directly influenced by the overall severity of the individual's symptoms. The rating is given on a score of 0 to 100 where higher scores indicate better functioning. Lastly, the NART provides a measure of premorbid IQ, that is, the level of performance that a patient might have attained if they had not been affected by an illness. The NART contains 61 words that a participant must read aloud and is scored based on whether the word was said correctly or

incorrectly. A score of 34 is indicative of an IQ of approximately 100 (McGrory, Austin, Shenkin, Starr, & Deary, 2015).

Each of the scales chosen have demonstrated good reliability and validity over time (Crawford, Parker, Stewart, Besson, & Lacey, 1989; Drake, Haddock, Tarrier, Bentall, & Lewis, 2007; Hilsenroth et al., 2000; Liechti, Capodilupo, Opler, Lawrence, & Yang, 2017; Opler, Yavorsky, & Daniel, 2017; Smith, Roberts, Brewer, & Pantelis, 1998). Data from the PANSS and SOFAS was collected by the patient's clinician; all other scales were collected by H.R or her graduate supervisor, D.F. Lastly, antipsychotic medication and dosage of the EPP group were converted to chlorpromazine equivalents (Woods, 2003) to allow for comparisons.

2.4 Procedure

The study was approved by the Nova Scotia Health Authority Research Ethics Board and written consent was obtained from all participants. Electrophysiological recordings were conducted at the BIOTIC Neuroimaging Research Laboratory located at the QEII Health Sciences Centre in Halifax, Nova Scotia. After signing the consent form, participants were interviewed on the required scales (i.e., NART, BNSS, and PSYRATS), informed on how the EEG system works, and were then asked to sit in a sound-proof booth and watch a silent emotionally-neutral movie without subtitles while the paradigms were being implemented. A hearing test was first conducted to ensure normal hearing ability (tones presented at 1000hz at 30, 25, and 20dB; 2000hz at 30, 25, and 20dB).

2.5 EEG Recordings and ERP Computation

Electrical activity was recorded and analyzed using BrainVision PyCorder software

(Brain Products GmbH, Gilching, DE). 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 [Fz], central [Cz], parietal [Pz]); three left hemisphere (frontal [F3], central [C3], parietal [P3]) and three right hemisphere (frontal [F4], central [C4], parietal [P4]) scalp sites (see Figure 5). Electrodes were also be placed on the mid-forehead and mastoids to serve as ground and reference, respectively. Bipolar recordings of horizontal and vertical electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 10kΩ. Offline data was filtered with an amplifier bandpass of 0.1 and 30Hz, digitized at 500Hz. The peak detection window for MMN was chosen based on visual inspection of the data at 100-220ms at Fz because this is the site of maximum amplitude.

2.6 Power Analysis

To determine the appropriate sample size needed in order to observe differences between the EPP and HC group, a power analysis was performed using G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009). As there is no current literature with the same paradigms and groups to obtain an approximate effect size from, this power analysis was performed post-hoc. The calculation was performed based on an observed power of .80 with a significance criterion of alpha = .05, and the effect sizes were calculated using MMN amplitudes at site Fz (see Appendix). Of note, samples of 15-20 per group are typical in ERP research and offer sufficient power due to the multiple repeated trials that are taken with the methodology. Thus, we proposed to recruit a total of 36 participants per group to ensure sufficient power while

allowing for the potential of outliers, unusable data, and other issues that may require us to drop participants from the analysis.

2.7 Data Analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences (Version 25; SPSS; IBM Corp., Armonk NY). Data from each paradigm were analyzed separately; specifically, the analysis of amplitude (the maximum displacement from equilibrium) and latency (the time of peak amplitude at Fz; the site of maximal amplitude). Data from posterior sites were not analyzed as these were used only to aid in the measurement of MMN topography. Analysis of amplitudes for each deviant type involved a one-way repeated measures ANOVA with three levels (group [EPP, HC], site [left/3, midline/z, right/4], and region [frontal, central, parietal]). Analysis of latencies involved an independent samples t-test. Correlational analyses were performed to examine the relationship between clinical measures (i.e., PANSS, PSYRATS, BNSS, SOFAS) and neurophysiological variables (i.e., MMN amplitudes and latencies) for the EPP group. Spearman's Rho correlation coefficient was used as the data is not normally distributed. Where applicable, Hedges' *g* was used as a measure of effect size, which takes into account the small and uneven sample sizes. Additional exploratory sex-based analyses using ANOVA were performed to determine if sex moderated the relationship between participants and MMN.

Chapter 3: Novelty Paradigm

The novelty paradigm includes a unique novel component dissimilar from the standard and deviant stimuli in which an environmental sound is integrated. Distinguishing between what is novel and what is not encompasses fundamental processes that enable an individual to appropriately react to stimuli in the environment, and as such is seen as a fundamental cognitive ability (Friedman et al., 2001). Because the novelty paradigm involves more complex stimuli, it is aimed to probe more so at the frontal generators of MMN than the temporal generators (Friedman et al., 2001). Furthermore, the novelty paradigm has high ecological validity as it closely resembles real world involuntary attention to novel events (Fisher, Smith, Labelle, & Knott, 2014; Friedman, Cycowicz, & Gaeta, 2001). We hypothesized that the EPP group would exhibit reduced MMN amplitudes relative to the HC group.

3.1 Test Battery

800 tones in four blocks were presented (200 per block). Each block consisted of 160 standard tones (1000Hz, 70dB, 336ms, probability = .80), 20 deviant tones (700Hz, 70dB, 336ms, probability = .10), and 20 novel sounds (70dB, 336ms, probability = .10). The novel stimuli included, but were not limited to, sounds such as a baby cry, a duck quack, a whistle, etc. Interstimulus interval was 664ms, and stimulus-onset asynchrony was 1000ms.

3.2 Results

A total of 13 patients (8 males, 5 females) aged 19 to 35, and 33 healthy controls (17 males, 16 females) aged 18 to 33 were included in the final analysis. One participant was removed due to an abnormal hearing test and 10 participants were removed due to technical

difficulties during EEG recordings. Approximately 11% (n = 5) of the participants were left-handed. The participants were not identically matched based on sex and estimated premorbid IQ, but the two groups did not significantly vary on these characteristics. Table 1 presents the demographic and clinical information of all participants. Due to insufficient EPP sample size, only exploratory sex analyses were conducted to determine whether biological sex moderated the relationship between clinical status and MMN. The exploratory sex analysis was conducted on the EPP group independently, the HC group independently, and the EPP-HC group combined. Frontal and central sites (F3, Fz, F4, C3, Cz, C4) were chosen for analysis as they best represent the topography of MMN.

3.2.1 Amplitude. The average amplitudes were not significantly different between groups (Table 2). For deviant stimuli, we found a main effect of region, $F(1,44) = 9.10$, $p = .004$, $g = .24$, in which frontal amplitudes were larger than central (M = -3.90μV, SD = 3.89μV; M = -3.10, SD = 2.80) (Table 3 and Figure 6).

3.2.2 Latency. For deviant stimuli, we observed group differences $t(44) = 2.17$, $p = .038$, $g = .60$, in which the mean latency for HCs (M = 171.64ms, SD = 29.76) was greater than for the EPP group (M = 154.00ms, SD = 22.60) (Table 5 and Figure 8). No main effects were found for novel stimuli.

3.2.3 Correlations. There were significant correlations between the EPP group and the BNSS subscales of asociality at sites Fz ($r = -.64$, $p = .017$) and Cz ($r = -.71$, $p = .007$) for novel stimuli, with distress at site F3 ($r = .58$, $p = .039$) for deviant stimuli, and for blunted affect at site C3 ($r = .59$, $p = .033$). Several correlations between MMN amplitudes to deviant stimuli for the EPP group and the overall SOFAS score were also found at sites Fz ($r = -.68$, $p = .031$); F4 ($r = -.72$, $p = .020$); C3 ($r = -.68$, $p = .031$); Cz ($r = -.76$, $p = .010$;) and C4 ($r = -.74$, $p = .015$).

Refer to Tables 6 and 7 for correlations. Due to a significant latency result, we ran an additional correlational analysis to determine if latency for MMN elicited by deviant stimuli was associated with certain variables for the EPP group (Table 8). A significant correlation was found between the deviant latency and PSYRATS total score (r = -.61, p = .028).

3.2.4 Exploratory Sex Analysis. There were no significant sex differences (see Table 9). We found main effects of region, in which frontal amplitudes were larger than central, in the HC group, F(1,31) = 10.64, p = .003 (M = -4.07μV, SD = .66; M = -3.10μV, SD = .46), and in the EPP-HC group combined, F(1,44) = 12.81, p = .001 (M = -3.99μV, SD = .52; M = -3.13μV, SD = .37), which is consistent with MMN topography.

3.2.5 Power Analysis. The observed power of between-group differences for deviant stimuli was .06, while the observed power of between-group differences for novel stimuli was .14. A post-hoc sample size analysis using observed effect size suggested that a minimum sample size of 2,422 participants for deviant stimuli, and 380 participants for novelty stimuli, would be required to observe a significant difference between EPP and HC samples (see Appendix).

3.3 Summary. Overall, we observed larger MMN amplitudes in the frontal region than central across both groups for deviant stimuli, as well as a longer latency in the HC group compared to the EPP group. We also found several correlations between the MMN amplitudes and asociality, distress, and overall SOFAS score in the EPP group.

Chapter 4: Emotional Paradigm

It has been found that healthy females respond more accurately to emotional vocal stimuli than males, suggesting that females may recruit additional processing resources when auditory change is emotional (Lithari et al., 2010; Schirmer et al., 2007; Schirmer et al., 2005). Considering that this finding has not been researched in EPP, by using this paradigm we intended to expand on research examining sex differences in ERP methodology and determine whether vocal-change detection sex differences exist among individuals with EPP. Thus, we hypothesized that females in both the EPP and control group would exhibit larger MMN amplitudes in response to the emotional stimuli and vocal change compared to males, and that the EPP group would exhibit reduced MMN amplitudes relative to the HCs overall.

4.1 Test Battery

Participants were presented with the syllables "dada" (stimulus length = 557ms) spoken in a neutral voice by a female speaker as well as the same syllables spoken by the same female speaker but with an angry intonation (stimulus length = 557ms). All stimuli were presented at 70dB in two blocks, with 1050 standards (neutral stimuli; probability = .875) and 150 deviants (angry stimuli; probability = .125) per block. The interstimulus interval was 443ms, and stimulus-onset asynchrony was 1000ms.

4.2 Results

A total of 13 patients (8 males, 5 females) aged 19 to 35, and 33 healthy controls (17 males, 16 females) aged 18 to 33 were included in the final analysis. One participant was removed due to an abnormal hearing test and 10 participants were removed due to technical

difficulties during EEG recordings. Approximately 11% (n = 5) of the participants were left-handed. The participants were not identically matched based on sex and estimated premorbid IQ, but the two groups did not significantly vary on these characteristics. Table 1 presents the demographic and clinical information of all participants. Due to insufficient EPP sample size, only exploratory sex analyses were conducted to determine whether biological sex moderated the relationship between clinical status and MMN. The exploratory sex analysis was conducted on the EPP group independently, the HC group independently, and the EPP-HC group combined. Frontal and central sites (F3, Fz, F4, C3, Cz, C4) where chosen for analysis as they best represent the topography of MMN.

4.2.1 Amplitude. The average amplitudes were not significantly different between groups (Table 2). We found main effects of region, $F(1,44) = 8.67$, $p = .005$, $g = .194$, in which frontal amplitudes were larger (more reduced) than central (M = -2.83μV, SD = 3.89; M = -2.18μV, SD = 2.80) across both groups (Table 4 and Figure 7).

4.2.2 Latency. No effects of latency were found (see Table 5).

4.2.3 Correlations. No significant correlations were found (see Tables 6 and 7).

4.2.4 Exploratory Sex Analysis. There were no significant sex differences (see Table 10). We found main effects of region, in which frontal amplitudes were larger than central, in the EPP group, $F(1,11) = 5.29$, $p = .042$ (M = -2.87μV, SD = 1.11; M = -2.00μV, SD = .87), and in the EPP-HC group combined, $F(1,44) = 7.66$, $p = .008$ (M = -2.87μV, SD = .413; M = -2.31μV, SD = .341) which is consistent with MMN topography.

4.2.5 Power Analysis. The observed power of between group differences for deviant (angry) stimuli was .05. A post-hoc sample size analysis using observed effect size suggested

that a minimum sample size of over two million participants would be required to observe a significant difference between EPP and HC samples (see Appendix).

4.3 Summary

Overall, we observed that MMN amplitudes in the frontal region were larger than those in central regions across both groups. There were no MMN differences between EPP and HCs using this paradigm and no latency, correlational, or sex difference effects were found.

Chapter 5: Discussion

5.1 Primary Outcomes

5.1.1 Amplitude and Latency. Based on previous research, we hypothesized that the EPP group would exhibit reduced MMN amplitudes relative to their HC counterparts in both paradigms, which was not supported. Although we did have low power, based on our post-hoc power analysis (see Appendix) the required minimum sample size needed to observe any significant differences between groups was exceedingly large, thus we determined that no differences between the two groups genuinely exist and this effect would remain if we had a larger sample. Additionally, because the NART score of the EPP group did not significantly differ from the control group, and their SOFAS score is relatively high, it is conceivable that our EPP group is functioning at a level near controls which may contribute to why there are no significant differences between the two groups. Relatedly, social and occupational functioning has been linked to MMN in schizophrenia, with better functioning associated with larger MMNs (Kawakubo & Kasai, 2006; Light & Braff, 2005a; Light & Braff, 2005b; Rasser et al., 2011).

We also hypothesized that females in both the EPP and HC group would exhibit larger MMN amplitudes in response to the angry stimuli, compared to males, in the emotional paradigm. This hypothesis was likewise not supported. We did, however, observe that MMN amplitudes across both groups in both paradigms were larger (i.e., more negative) in the frontal region and weakened as it moved back towards the central region of the cortex, which is consistent with the literature on MMN topography.

Interestingly, we found that within the novelty paradigm, the EPP group had shorter latencies than the HC group in response to the deviant stimuli, implying that those with EPP distinguished the deviant stimuli quicker than the HCs. In other research studies examining

MMN and schizophrenia, very little has been reported regarding differences in latencies between HC and patient groups. One study found that shorter MMN latencies in those with schizophrenia was associated with greater severity of positive symptoms (Grzella et al., 2001), while another found that shorter latencies were associated with poorer verbal memory performance (Kärgel, Sartory, Kariofillis, Wiltfang, & Müller, 2014). Due to the minimal research and discrepancies on the topic, we can only speculate as to what occurred with our participants. Post-hoc correlational analysis revealed a significant negative relationship between MMN latencies to deviant stimuli and PSYRATS total score for the EPP group, implying that shorter latencies are associated with increased trait measures of auditory hallucinations, a positive symptom, which does relate to the study mentioned earlier conducted by Grzella et al. Moreover, the shorter latency was only associated with the pure-tone deviant stimulus, rather than the environmental sound/novel deviant stimulus. As the pure-tone deviant is the simplest of the two deviant stimuli, our results suggest that the MMN response to pure-tone deviants may be more easily distinguished than environmental sound deviants.

5.1.2. Correlations. Within the EPP group, we found several correlations between ERP measures and subscales on the BNSS. Specifically, increased asociality (a lack of motivation to engage in social interaction) blunted affect, and distress were associated with a greater reduction in MMN relative to the other EPP participants, suggesting a possible relationship between these negative symptoms and neurocognitive deficits. Distress is not generally considered a negative symptom; however, when the BNSS scale was developed the researchers found that removing the distress factor did not have a significant change in the internal consistency of the scale (Kirkpatrick et al., 2011). To support result, a number of studies have found that the negative symptoms in schizophrenia could potentially be classified into primary and secondary; primary

being those fundamental to the illness (i.e., anhedonia, apathy, alogia, etc.), while secondary symptoms are brought on by the positive symptoms (i.e., depression, distress, akinesia) (Kirschner, Aleman, Kaiser, 2017; Kirkpatrick, 2014; Peralta, Cuesta, Martinez-Larrea, & Serrano, 2000). Furthermore, measures of distress have been used alongside negative symptom scales to delineate patient groups with and without "primary" negative symptoms with good validity (Kirktpatrick et al., 2010). The relationship found between negative symptoms and neurocognitive deficits in schizophrenia is not unusual, but whether their relationship indicates that the two are intrinsically related is not certain (Harvey, Koren, Reichenberg, & Bowie, 2006).

The correlations our study found between MMN reduction and negative symptoms is not surprising, considering the persistence of negative symptoms despite receiving adequate treatment. As MMN is an indirect indication of neurocognitive functioning, our results provide more support for the connection between negative symptoms and cognitive deficits. It has also been reported that negative symptoms are more prominent in early psychosis (Mäkinen et al., 2008), compared to chronic schizophrenia, and as such the correlations found may be more relevant to those with EPP.

Lastly, we also found correlations between the EPP group and their total SOFAS score; the better score the patients had on their social and occupational functioning, the less reduced their MMN waveform. This finding suggests that individuals who function well in their daily lives tend to have better neurocognitive functioning than individuals who do not. Moreover, adhering to a treatment regimen and maintaining a good support system outside the clinic are also important in helping to counter the degree of cognitive deficits observed. Furthermore, the mean SOFAS score of our patient group represents no more than a slight impairment in social, occupational, or educational functioning. Compared to recent studies of EPP and first-episode

psychosis (Chong et al., 2018; Higuchi et al., 2017), our mean SOFAS score is considerably high, which may explain the lack of differences seen between our two groups; as our EPP group is functioning at a level near comparable to controls, then there are no significant differences in functioning to observe. However, it is important to note that this is only in regard to social and occupational functioning, as we did not measure current cognitive functioning of either group. Additionally, the association between the MMN reduction and SOFAS score is likely bidirectional such that poor neurocognitive functioning can lead to undesirable daily functioning.

5.1.3 Exploratory Sex Analyses. We were hoping to discern whether sex moderated the effect of MMN and EPP, but due to a small sample size in our EPP group, only exploratory analyses were conducted. No significant sex differences were found between the EPP-HC group or within the EPP group. Our sample size within the HC group was large enough to support that no sex differences exist between healthy males and females in our study.

As mentioned previously, biological sex needs to be taken into account as a potentially influential factor if we are to gain a comprehensive understanding of MMN and schizophrenia. Nevertheless, the existing literature on this topic has been significantly lacking, which appears to be due to researchers not considering sex as an influential factor or simply not disseminating results because they found no significant conclusions (Riel et al., 2019). By understanding sex differences in schizophrenia, clinicians will have the ability to tailor treatments for males and females to improve clinical outcomes. As such, future research in MMN would benefit from implementing sex as variable and reporting on the results regardless of the outcome.

5.2 Study Limitations

There are limitations that should be noted within the study. First, we had a slightly

smaller sample size in the EPP group than expected, which resulted in lowered power and the inability to conduct formal sex-based analyses. Second, we did not discern whether individuals in the EPP group could actually distinguish between angry vs. neutral intonations in the emotional paradigm; however, that fact that we observed a MMN implies that participants were able to distinguish between the two stimuli. Third, our groups were not identically matched based on sex and premorbid IQ, so biological discrepancies between participants may have influenced the results. Fourth, we did not screen for participants who had a first degree relative with schizophrenia, so potentially "at risk" controls may have been included.

5.3 Study Strengths

There are several strengths to be noted from this study. First, this study was the first to implement a novelty paradigm with an EPP group, which is unique among MMN literature and provides insight to the relationship between schizophrenia and environmental sounds. Second, by including an emotional paradigm aimed to elicit sex differences in MMN, we added to the lack of EEG research on this topic, at least within healthy controls. Third, our study included MMN paradigms with complex stimuli which provides a different examination of auditory detection in EPP compared to simple stimuli paradigms. Fourth, our study implemented valid and reliable clinical measures including the use of the SOFAS, which unlike the global assessment of functioning scale, is not directly influenced by the severity of the individual's symptoms and thus represents a more precise view of social and occupational functioning. Fifth, as the reduction of MMN is specific to those with schizophrenia, we put great effort in ensuring that our EPP group best represented those with schizophrenia rather than schizoaffective disorder or other psychotic-related illnesses.

5.4 Future Directions

Why MMN deficits occur in schizophrenia is not well understood, but there may be a connection between MMN and the dendritic abnormalities found from in vivo studies of individuals with schizophrenia, considering that grey matter volume loss occurs in the transverse temporal gyrus which constitutes the auditory cortex – the generator of MMN. Moving forward, the associations between MMN and gray matter volume reduction provides an area of research opportunity in latent biological mechanisms underlying schizophrenia, as well as in early pharmacological treatments in preventing progressive neural deterioration of the illness. The link between MMN and glutamate further suggests that NMDA receptor-modulating agents could be another intervention for individuals with schizophrenia. This appears to be a very promising area of research considering that original dopaminergic models of schizophrenia only appear to account for the positive symptoms, whereas glutamatergic models are more comprehensive in accounting for both negative and neurocognitive symptoms and thus may serve as a better etiological model for schizophrenia as a whole (Javitt, 2010). Additionally, considering the associations that our study, along with others, found between MMN reduction and negative symptoms supports existing efforts for interventions to better manage persistent negative symptoms. Longitudinal studies of MMN in EPP would also be ideal in further understanding MMN's use as an indicator of illness progression, as well as studies identifying factors that may moderate MMN's utility, as such biological sex. This will prove to be important in helping to predict, diagnose, and monitor schizophrenia in affected individuals.

5.5 Conclusions and Implications

Although our study did not demonstrate any significant patient-control differences, the

disruption of basic auditory processing has been established in chronic schizophrenia, and as such, interventions targeting basic auditory skills indicated by MMN could improve functioning and quality of life for patients. One such example is auditory cognitive training whereby participants engage in intensive and adaptive tasks that are thought to improve auditory perception (Perez, Miyakoshi, Makeig, & Light, 2019). A recent study that implemented auditory-based targeted cognitive training on individuals with schizophrenia found that after only one hour of training there was an attenuation of the MMN waveform (Perez et al., 2019). This result signifies plasticity within the cortical structures that generate MMN, and as such, interventions targeting cortical plasticity may be suitable treatment options for individuals with schizophrenia.

The idea that more complex-based stimuli paradigms may better clarify MMN deficits in EPP than simple stimuli might no longer be tenable. However, it is conceivable that, regardless of the paradigm complexity, MMN may be more appropriately used as an indicator of illness progression and symptomology, rather than for use of identifying at-risk individuals. As such, the clinical implication of this study suggests that MMN as a biomarker for schizophrenia may be more useful in combination with other potential biomarkers, rather than on its own.

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Table 1

Demographic and clinical data of participants

	EPP	HC
	Mean (SD) or *n* (%)	Mean (SD) or *n* (%)
Age (years)	25.00 (5.02)	23.76 (4.08)
NART score	32.54 (10.47)	37.94 (9.08)
Sex		
Male	8 (61.54)	17 (51.52)
Female	5 (38.46)	16 (48.48)
Handedness		
Left	1 (7.69)	4 (12.12)
Right	12 (92.31)	29 (87.88)
Chlorpromazine equivalents[a]	230.62 (119.50)	
SOFAS score[b]	71.30 (8.63)	
PSYRATS total score[c]	19.89 (4.43)	
PANSS		
General	23.50 (2.27)	
Positive	10.70 (2.83)	
Negative	11.60 (3.13)	
BNSS		
Distress	2.62 (1.89)	
Avolition	1.50 (1.53)	
Anhedonia	8.69 (6.05)	
Asociality	1.88 (1.28)	
Blunted affect	3.46 (1.60)	
Alogia	4.00 (2.77)	

[a] Presented in daily dosages.
[b] Missing data from three individuals.
[c] Missing data from four individuals.

Table 2

Mean amplitude and latency of participants

	Emotional Paradigm: Angry Stimuli		Novel Paradigm: Deviant Stimuli		Novel Paradigm: Novel Stimuli	
	HC	EPP	HC	EPP	HC	EPP
F3	-2.73μV	-2.66μV	-3.80μV	-3.58μV	-3.13μV	-1.28μV
Fz	-2.94μV	-2.93μV	-4.29μV	-3.88μV	-2.94μV	-1.74μV
F4	-2.92μV	-2.81μV	-4.08μV	-3.77μV	-2.86μV	-1.37μV
C3	-2.29μV	-1.53μV	-3.12μV	-2.62μV	-3.09μV	-2.05μV
Cz	-2.67μV	-2.27μV	-3.07μV	-3.24μV	-3.13μV	-2.22μV
C4	-2.34μV	-1.95μV	-3.10μV	-3.43μV	-2.16μV	-0.92μV
Latency (Fz)	165.58ms	155.85ms	171.64.ms*	154.00ms*	144.61ms	143.23ms

Note. μV = microvolts; ms = milliseconds
*$p < .05$ (two-tailed).

Table 3

Main effects of the novelty paradigm

	Deviant Stimuli			
	df	Mean Square	F	Sig
Region	1, 44	36.27	9.10	.004*
Region * Group	1, 44	1.42	.36	.55
Site	2, 67	3.51	1.32	.27
Site * Group	2, 67	.84	.32	.67
Region * Site	2, 77	.37	.50	.59
Region * Site * Group	2, 77	1.43	1.93	.16
	Novel Stimuli			
	df	Mean Square	F	Sig
Region	1, 44	.09	.01	.91
Region * Group	1, 44	2.84	.44	.51
Site	2, 73	11.92	2.52	.10
Site * Group	2, 73	.96	.20	.78
Region * Site	2, 66	7.06	2.28	.12
Region * Site * Group	2, 66	.59	.19	.76

Note: Greenhouse-Geisser was used to account for sphericity violation.
*$p < .05$ (two-tailed).

Table 4

Main effects of the emotional paradigm

	df	Mean Square	F	Sig
Region	1, 44	24.17	8.67	.005*
Region * Group	1, 44	2.92	1.05	.31
Site	2, 71	3.74	2.84	.08
Site * Group	2, 71	.29	.22	.76
Region * Site	1, 77	.60	2.73	.08
Region * Site * Group	2, 77	.25	1.12	.33

Note: Greenhouse-Geisser was used to account for sphericity violation.
*$p < .05$ (two-tailed).

Table 5

Latencies for the novelty and emotional paradigm

				Confidence Interval	
	t	df	Sig	Lower Bound	Upper Bound
Novelty Paradigm: Deviant Stimuli	2.17	29	.04*	1.01	34.27
Novelty Paradigm: Novel Stimuli	.16	38	.87	-15.60	18.35
Emotional Paradigm: Angry Stimuli	.63	23	.53	-22.12	41.58

Note: Equal variances not assumed.
*$p < .05$ (two-tailed).

Table 6

Novelty and emotional paradigm correlations for the EPP group on the BNSS

	Novelty Paradigm						
	Site	Asociality	Anhedonia	Affect	Avolition	Alogia	Distress
Novel Stimuli							
	F3	-.54	-.35	-.02	-.32	-.06	-.05
	Fz	-.64*	-.43	-.12	-.41	-.20	-.12
	F4	-.53	-.26	-.08	-.23	-.07	.05
	C3	-.61*	-.31	-.06	-.27	-.36	.06
	Cz	-.71*	-.37	-.12	-.36	-.37	-.08
	C4	-.64*	-.43	-.15	-.42	-.30	-.01
Deviant Stimuli							
	F3	.25	.28	.53	.30	.21	.58*
	Fz	.25	.24	.43	.26	.03	.42
	F4	.17	.28	.48	.32	.09	.46
	C3	.32	.51	.59*	.46	.12	.69**
	Cz	.41	.29	.27	.29	-.23	.48
	C4	.10	.13	.11	.24	-.05	.18
	Emotional Paradigm						
	Site	Asociality	Anhedonia	Affect	Avolition	Alogia	Distress
Angry Stimuli							
	F3	-.16	-.43	-.10	-.39	-.25	.16
	Fz	-.20	-.39	-.06	-.37	-.27	.18
	F4	-.29	-.38	-.09	-.40	-.32	.14
	C3	-.11	-.39	-.12	-.35	-.40	.24
	Cz	-.08	-.27	-.03	-.19	-.27	.26
	C4	-.09	-.26	-.02	-.19	-.31	.25

Note. Spearman's Rho correlations (two-tailed).
*$p < .05$
**$p < .01$

Table 7

Novelty and Emotional paradigm correlations for the EPP group on clinical scales

	Novelty Paradigm			
	Site	SOFAS	PSYRATS	PANSS
Novel Stimuli				
	F3	.30	-.18	-.06
	Fz	.21	-.10	.08
	F4	.08	.02	.15
	C3	-.28	.11	.26
	Cz	-.09	.13	.18
	C4	.03	.05	.07
Deviant Stimuli				
	F3	-.55	.03	.26
	Fz	-.68*	-.06	.38
	F4	-.72*	-.14	.38
	C3	-.68*	.12	.30
	Cz	-.76*	-.05	.51
	C4	-.74*	-.19	.51
	Emotional Paradigm			
	Site	SOFAS	PSYRATS	PANSS
Angry Stimuli				
	F3	-.23	.04	-.05
	Fz	-.27	.09	-.05
	F4	-.21	.16	-.06
	C3	-.26	.12	.02
	Cz	-.21	.20	.07
	C4	-.24	.22	.13

Note. Spearman's Rho correlations (two-tailed); total scores used.
*$p < .05$

Table 8

Novelty paradigm correlations for the EPP group of latency

	SOFAS	PSYRATS Total Score	PANSS Total Score	PANSS: Positive	PANSS: Negative	PANSS: General
Novel Latency	-.02	-.19	-.60	-.60	-.38	-.70
Deviant Latency	-.32	-.61*	.20	.28	.16	.09

Note. Spearman's Rho correlations (two-tailed); total scores used. Peak latency recorded at Fz.
*$p < .05$

Table 9

Exploratory sex analysis of the novelty paradigm with deviant and novel stimuli

	EPP Deviant Stimuli				EPP Novel Stimuli			
	df	Mean Square	F	Sig	df	Mean Square	F	Sig
Region	1, 11	5.62	1.61	.23	1, 11	3.96	1.38	.27
Region * Sex	1, 11	3.05	.87	.37	1, 11	13.54	4.71	.05
Site	1, 15	1.99	.52	.53	1, 13	6.00	1.34	.26
Site * Sex	1, 15	1.95	.51	.54	1, 13	1.74	.42	.57
Region * Site	1, 15	.62	.86	.40	1, 12	3.33	.83	.39
Region * Site * Sex	1, 15	.65	.90	.39	1, 12	2.63	.65	.44
	HC Deviant Stimuli				HC Novel Stimuli			
	df	Mean Square	F	Sig	df	Mean Square	F	Sig
Region	1, 31	45.94	10.64	.003*	1, 31	1.51	.20	.66
Region * Sex	1, 31	.02	.004	.95	1, 31	6.46	.85	.36
Site	2, 50	1.04	.43	.61	2, 54	8.07	1.15	.23
Site * Sex	2, 50	.08	.03	.94	2, 54	1.31	.25	.75
Region * Site	2, 44	1.43	1.79	.18	2, 52	4.00	1.38	.26
Region * Site * Sex	2, 44	.97	1.21	.30	2, 52	3.39	1.17	.31
	EPP and HC Deviant Stimuli				EPP and HC Novel Stimuli			
	df	Mean Square	F	Sig	df	Mean Square	F	Sig
Region	1, 44	51.21	12.81	.001*	1, 44	.02	.003	.96
Region * Sex	1, 44	.82	.21	.65	1, 44	15.23	2.47	.12
Site	2, 67	2.70	1.01	.35	2, 73	12.39	2.63	.09
Site * Sex	2, 67	.87	.33	.66	2, 73	2.10	.45	.61
Region * Site	2, 78	.74	1.01	.36	2, 67	6.38	2.17	.13
Region * Site * Sex	2, 78	1.54	2.10	.14	2, 67	5.46	1.85	.17

Note: Greenhouse-Geisser was used to account for sphericity violation.
*$p < .05$ (two-tailed).

Table 10

Exploratory sex analysis of the emotional paradigm with angry stimuli

	EPP			
	df	Mean Square	F	Sig
Region	1, 11	14.09	5.29	.04*
Region * Sex	1, 11	.05	.02	.89
Site	2, 17	2.13	1.23	.31
Site * Sex	2, 17	.06	.03	.94
Region * Site	1, 13	.61	1.46	.26
Region * Site * Sex	1, 13	.31	.73	.43
	HC			
	df	Mean Square	F	Sig
Region	1, 31	9.28	3.12	.09
Region * Sex	1, 31	1.08	.36	.55
Site	1, 39	2.32	1.47	.24
Site * Sex	1, 39	.81	.51	.52
Region * Site	2, 56	.42	2.35	.11
Region * Site * Sex	2, 56	.49	2.73	.08
	EPP and HC			
	df	Mean Square	F	Sig
Region	1, 44	21.81	7.66	.008*
Region * Sex	1, 44	.37	.13	.72
Site	2, 71	3.66	2.79	.08
Site * Sex	2, 71	.39	.30	.70
Region * Site	2, 76	.66	2.96	.07
Region * Site * Sex	2, 76	.25	1.11	.33

Note: Greenhouse-Geisser was used to account for sphericity violation.
*$p < .05$ (two-tailed).

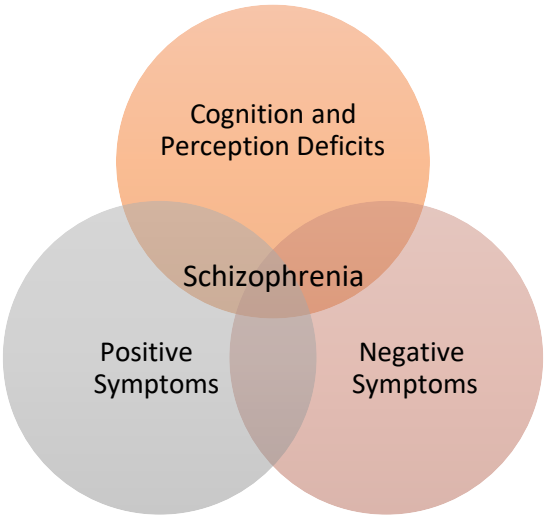

Figure 1. Illustration of how the core clusters of symptoms combine to give rise to the illness of schizophrenia.

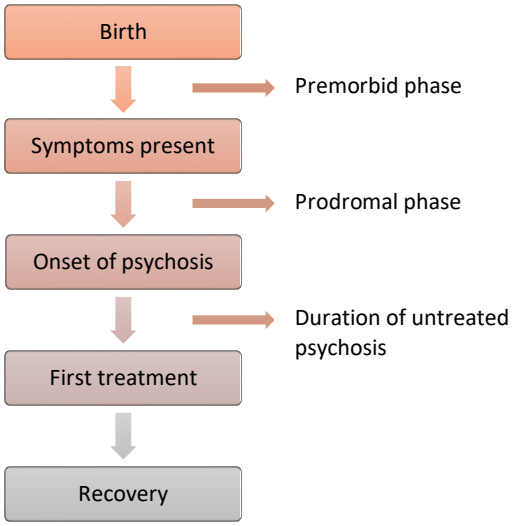

Figure 2. Schizophrenia as a phased illness.

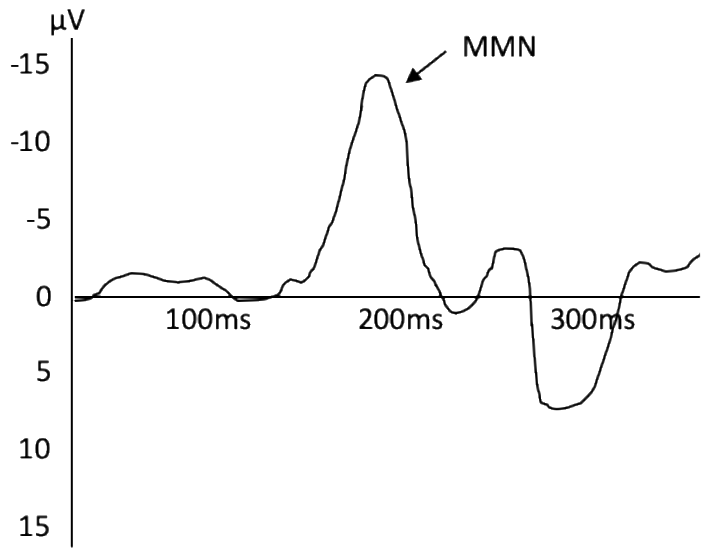

Figure 3. Illustration of the auditory mismatch negativity, an event-related potential occurring approximately 100-250ms after a deviant stimulus.

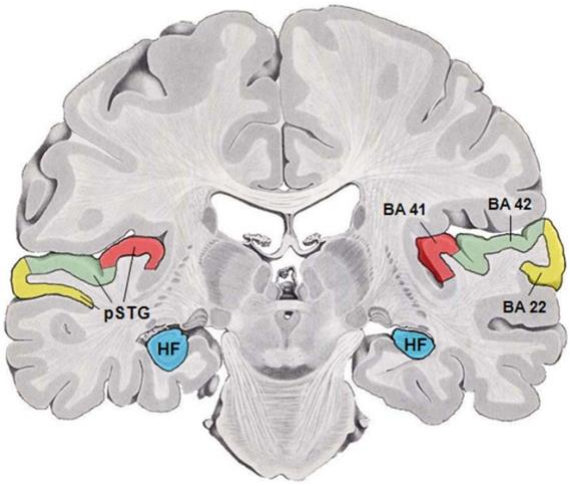

Figure 4. Coronal view of the auditory cortex in the human brain. BA 41 = Brodmann area 41/anterior transverse gyrus; BA 42 = Brodmann area 42/posterior transverse gyrus; BA 22 = Brodmann area 22/superior temporal gyrus.
Image retrieved from a creative commons licence initially published in Talbot et al. (2011). Synaptic dysbindin-1 reductions in schizophrenia occur in an isoform-specific manner indicating their subsynaptic location. PLoS ONE 6(3): e16886.

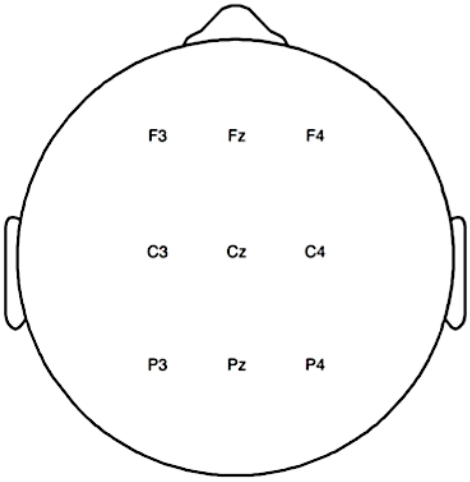

Figure 5. Primary scalp site locations: Three midline (Fz, Cz, Pz); three left hemisphere (F3, C3, P3) and three right hemisphere (F4, C4, P4).

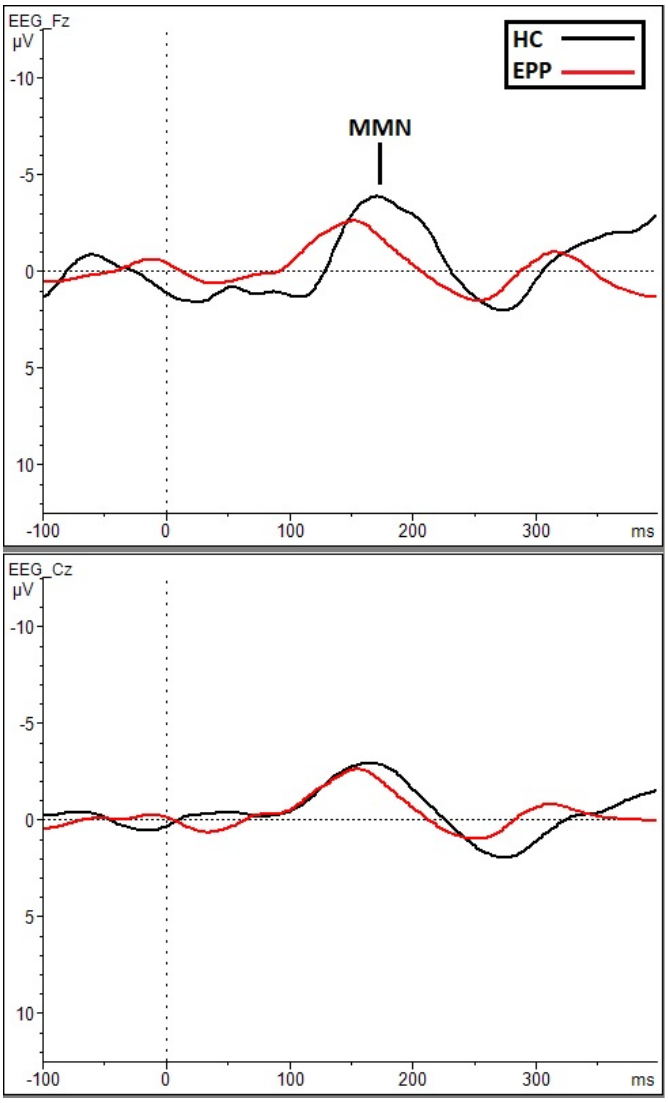

Figure 6. Novelty paradigm with deviant stimuli: Larger frontal MMN amplitudes than central across both groups.

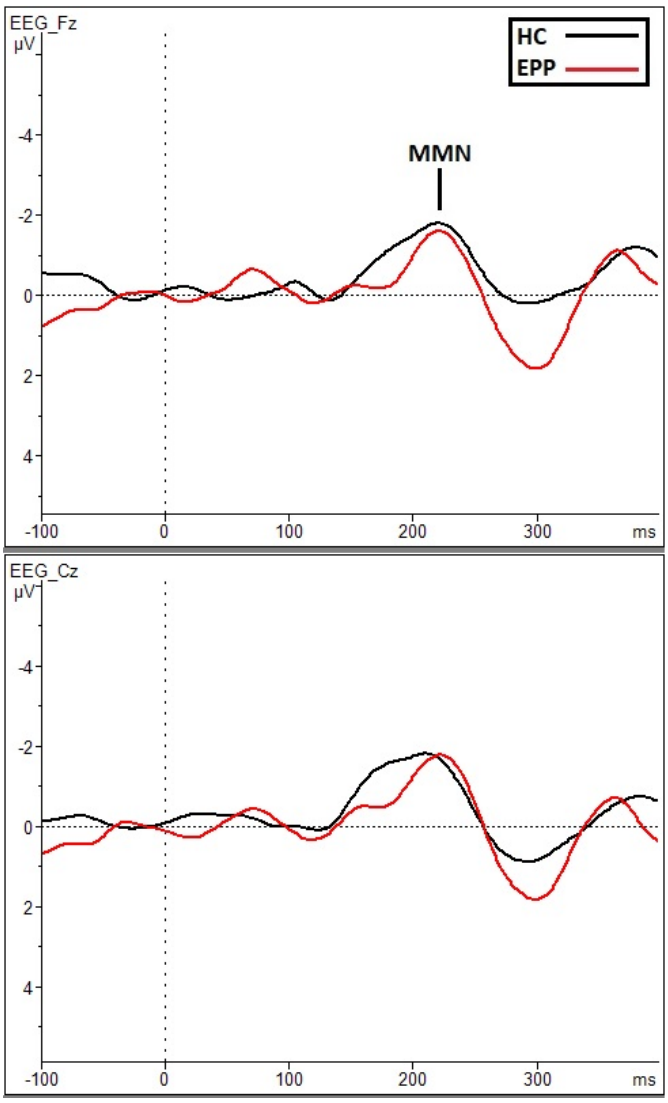

Figure 7. Emotional paradigm with angry stimuli: Larger frontal MMN amplitudes than central across both groups.

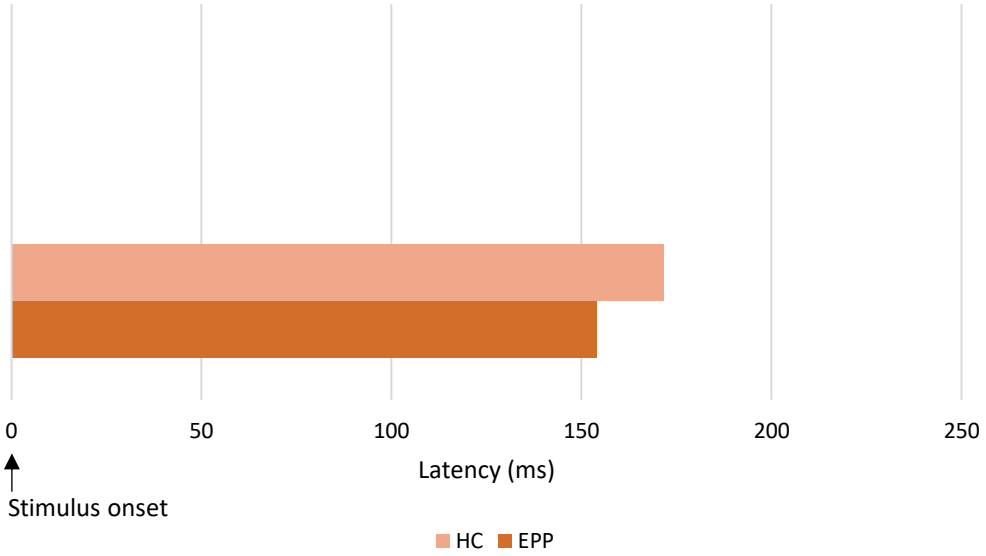

Figure 8. Latency of the novelty paradigm with deviant stimuli.

Appendix

Table A

Post-hoc power analysis reporting effect size and power from study, as well as required sample size needed to observe patient-control differences and sex differences within groups with a power of .80 and significance criterion of alpha = .05. Effect size taken from site Fz.

	EPP vs. HC	EPP Males vs. Females	HC Males vs. Females
	Novelty Paradigm: Deviant Stimuli		
Hedges' *g*	.11	.17	.15
Power	.06	.06	.07
Required Sample Size	2,422	1,112	1,388
	Novelty Paradigm: Novel Stimuli		
Hedges' *g*	.29	.01	.37
Power	.14	.05	.18
Required Sample Size	380	207,554	228
	Emotional Paradigm: Angry Stimuli		
Hedges' *g*	.003	.13	.19
Power	.05	.06	.08
Required Sample Size	2,107,136	1,764	846