Examining the Simple and Complex Mismatch Negativity in Early Phase Psychosis

by

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Abstract

Background: Using electroencephalography (EEG) to examine the simple mismatch negativity (MMN), a marker of auditory cortex function, has been of great interest in the exploration of biomarkers for psychotic illness. Despite many studies reporting MMN deficits in chronic schizophrenia, there are not reliable reports of MMN reductions in the early phase of the illness, suggesting the MMN is not a sensitive enough measure of vulnerability to be used as a biomarker. Recently, a more computationally complex measure of auditory cortex function (the complex mismatch negativity; cMMN) has been hypothesized to provide a more sensitive marker of illness vulnerability.

Methods: The current study employed a novel dual rule cMMN paradigm to examine the cMMN in 14 individuals with early phase psychosis (EPP) and 15 healthy controls (HC). Additionally, the MMN response to five deviant types was also recorded using the optimal multi-feature MMN paradigm in 13 individuals with EPP and 17 HC. Demographic variables, symptom severity, and measures of functioning were all collected to explore relationships with the neurophysiological variables.

Results: We found significant reductions of cMMN amplitudes at the site of maximal amplitude (Fz) in EPP (p = .017) with large effect sizes (*Hedges' g* = 0.96). We also found a reduction of MMN amplitudes in response to duration deviants in the left frontal region (p = .036, *Hedges' g* = 0.83). There were also correlations between more severe positive psychosis symptoms of auditory hallucinations (r = -0.582, p = .037) and unusual thought content/delusional ideas (r = -0.601, p = .030) and increased MMN amplitudes in response to duration deviants. Increased symptoms of unusual thought content/delusional ideas were also related to higher MMN amplitudes following gap (r = -0.558, p = .047) and location deviants (r = -0.590, p = .034). Positive psychosis symptoms of suspiciousness/persecutory ideas were related to a higher MMN in response to frequency deviants (r = -0.670, p = .012) and grandiose ideas were related to a higher MMN in response to gap deviants (r = -0.556, p = .049). Negative psychosis symptoms of social anhedonia were related to higher MMN amplitudes following duration (r = -0.790, p = .001) and frequency deviants (r = -0.625, p = .022), while reduced experience of emotions and self was related to higher MMN amplitudes following the location deviant (r = -0.603, p = .029). Additionally, there were significant correlations between higher cMMN amplitudes and more severe auditory hallucinations (r = -0.632, p = .015).

Discussion: This study is an early step in the exploration of the cMMN as a biomarker for psychosis risk and provides evidence that the dual rule cMMN paradigm shows promise as a method for cMMN elicitation. Future studies should utilize this paradigm to examine the cMMN in a sample of high-risk individuals while employing a longitudinal design to determine the predictive capability of this measure.

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Chapter 1: Introduction

1.1 Schizophrenia and Phases of Psychotic Illness Development

Schizophrenia is a psychotic disorder with a global lifetime prevalence of 1.0% that is characterized by disturbances in thought, perception, and behaviour (Saha et al., 2005). A survey completed in 2016 determined that 0.9% of the Canadian population and 0.6% of the Nova Scotian population were diagnosed with schizophrenia (Canadian Chronic Disease Surveillance System (CCDSS), 2019). In Nova Scotia, approximately 28 people per 1000 in the population are diagnosed with schizophrenia each year (Canadian Chronic Disease Surveillance System (CCDSS), 2019). The estimated direct economic cost of schizophrenia in Canada is approximately two billion dollars each year, and when considering productivity and work losses that number increases to over six billion dollars each year (Goeree et al., 2005).

Schizophrenia spectrum disorders typically develop in stages. Prior to the presence of symptoms that exceed a clinical threshold, sub-clinical (or prodromal) psychotic symptoms can occur. Typically, when occurring between the ages of 14-29, these prodromal symptoms classify an individual as being at clinical high risk (CHR) for developing psychosis (Yung & McGorry, 2007). Even at this early stage, CHR individuals show cognitive impartments like deficits in working memory (Brewer et al., 2005). The average age of psychosis onset usually occurs in late adolescence or early adulthood and is referred to as the first episode of psychosis (FEP). The first five years following an individual's FEP is referred to as early phase psychosis (EPP). The EPP is a critical time because a longer length of untreated psychotic illness during this time is related to worse functional and symptomatic outcomes in the individual (Malla & McGorry, 2019; Penttilä et al., 2014; Perkins et al., 2005). This stresses the criticality and importance of appropriate intervention during this time. Following this critical EPP period, an individual can be

classified as being in the chronic phase of the illness. Psychosis has the potential to be devastating to an individual's future social and occupational functioning (Cowman et al., 2021). Approximately 50% of patients who go on to develop chronic schizophrenia will not return to work following their first hospitalization (Racenstein et al., 2002).

The etiology of psychosis has complex genetic contributions, and there is no one gene variation responsible. In fact, it is likely that thousands of common gene variants contribute to the genetic liability of psychosis (Ng et al., 2009; Zwicker et al., 2018). The environment of the individual can also interact with and influence the expression of the genome, resulting in an area of research that has been rapidly expanding in interest focusing on how epigenetics can influence psychosis risk (Cromby et al., 2019). The lifetime risk of developing schizophrenia if you are a monozygotic twin of an affected individual is 33%, which emphasizes the significant genetic contribution to its etiology, but also suggests non-genetic contributors as well (Cardno et al., 1999; Hilker et al., 2018). Nonetheless, if you have a first-degree family member with psychosis, you can be classified as genetically high-risk (GHR) for developing the illness. Those who are GHR have approximately a 10% chance of developing psychosis themselves (McIntosh et al., 2011).

While the exact cause of schizophrenia is unknown, a mixture of biological and environmental factors is assumed to play a role in the development. A prominent theory on the underlying biological basis of schizophrenia includes the disconnection hypothesis, which posits that schizophrenia is fundamentally a failure of proper functional integration throughout the brain (Friston, 1999). This hypothesis is widely supported by neuroimaging studies that report functional dysconnectivity across multiple regions of the cortex in schizophrenia (for review see Zhou et al., 2015).

Two theories on the biological causes of schizophrenia that have been debated include viewing the disorder as a neurodevelopmental, or a neurodegenerative illness. Neurodegenerative theories suggest there are degenerative changes that occur in the brain following illness onset. This hypothesis first emerged when Kraepelin described schizophrenia as “dementia praecox”, which insinuated that there would be a progressive and chronic decline in the individual. The neurodegenerative hypothesis was later supported by longitudinal neuroimaging studies that did indeed show changes in neuronal structure following illness onset (Shenton et al., 2001). However, these claims have since been refuted, as more recent imaging studies show that the majority of the neurodegeneration that occurs with schizophrenia can be seen before, or concurrently with illness onset (Pantelis et al., 2003; Rund, 2009).

On the other hand, neurodevelopmental theories suggest that one or more factors disrupt the course of normal neural development, which then leads to the development of psychosis. Within this line of thought, the two-hit hypothesis states that individuals who are genetically vulnerable and undergo one distinct developmental insult early on in the course of development (e.g. in utero) are primed for a later developmental insult that ultimately leads to the development of psychosis (Bayer et al., 1999). More recently, it has been suggested that more than two “hits” can contribute to the development of the illness, particularly when these “hits” occur during key periods of neurodevelopment like prenatally or during adolescence (Davis et al., 2016).

Environmental factors that can increase one’s risk of developing psychosis can occur at all stages of development. In utero, increased markers of inflammation in the mother are associated with an increased risk of psychosis (Canetta et al., 2014), and increased levels of anti-inflammatory markers are associated with a decreased risk (Allswede et al., 2016). In childhood,

being a victim of bullying at school can increase your chances of developing psychotic symptoms by age 18 (Wolke et al., 2014). Additionally, individuals with psychosis report experiencing high rates of adverse life events and childhood trauma (Bonoldi et al., 2013; Duhig et al., 2015), partially implicating the role of trauma in the development of psychosis and stressing the importance of examining trauma in psychosis research (Schäfer & Fisher, 2022).

Other environmental risk factors that occur later in development are substance use-related (Zwicker et al., 2018). The use of methamphetamine is related to increased transient psychotic symptoms(McKetin et al., 2016), and those who are GHR and partake in methamphetamine use (or who are prescribed stimulants) are at an even greater risk than GHR individuals who do not (Li et al., 2014; MacKenzie et al., 2016). There is also vast and compelling evidence that suggests cannabis use greatly increases an individual's risk of developing psychosis, where earlier age of use and higher dosage equates to greater risk (Di Forti et al., 2009, 2014, 2019; Gage et al., 2016; Henquet et al., 2008, 2008; Marconi et al., 2016; Murray et al., 2016, 2017; Stefanis et al., 2013; Stepniak et al., 2014). Additional environmental risk factors include tobacco use before the age of 15, and residing in urban areas (McGrath et al., 2016; Vassos et al., 2012).

1.2 The Importance of Early Intervention Services for Psychosis

Early intervention and a shorter duration of untreated psychosis following the FEP can greatly improve long-term outcomes, including antipsychotic treatment response (thus symptomatic outcomes) as well as functional outcomes (Grawe et al., 2006; Hastrup et al., 2013; Insel, 2010; Kuipers et al., 2004; Malla & McGorry, 2019; Perkins et al., 2005; Ruggeri et al., 2015; Srihari et al., 2015). A recent meta-analysis that compared randomized control trials of early intervention services to standard treatment practices found early intervention resulted in

superior outcomes across multiple clinical variables such as the required number of hospitalizations, psychosis symptoms, social and occupational functioning, and overall quality of life (Correll et al., 2018). Further, these reported benefits of early intervention services may be underestimated still due to research design constraints (Malla & McGorry, 2019). Early intervention services for psychosis in Canada started in the 1990s, and now there are specialized early phase psychosis clinics across the nation (Iyer et al., 2015). Early intervention services for psychosis have high cost-effectiveness and are undeniably an important part of the scope of care for psychosis (Hastrup et al., 2013; Valmaggia et al., 2009). Further, some evidence suggests interventions like pharmacological treatment in combination with psychotherapy can even reduce the risk of converting to psychosis in a CHR sample (McGlashan et al., 2006; McGorry et al., 2002; McGorry & Mei, 2018; Zhang et al., 2020). Accordingly, identifying individuals who are at-risk as early as possible and providing these interventions is critical (Kahn et al., 2015).

Approximately 29-36% of CHR individuals will go on to develop psychosis, and the presence of prodromal symptoms may signify the development of a mental illness other than psychosis, such as bipolar disorder (Fusar-Poli et al., 2013; Rössler et al., 2011). The proportion of GHR individuals who will develop psychosis is even lower at approximately 10% (McIntosh et al., 2011). Although there is evidence to suggest interventions in at-risk groups can reduce the risk of the development of psychosis (McGlashan et al., 2006; McGorry et al., 2002; McGorry & Mei, 2018; Zhang et al., 2020), employing specific interventions (like antipsychotic medication) can provide unwelcome side effects that would ideally be avoided if not completely necessary (Stroup & Gray, 2018). This underscores the need in our health care system for a more sensitive tool to identify at-risk individuals for psychosis development than just prodromal symptoms or genetic risk alone. If a measure with higher sensitivity could be employed, we could ensure

stage-appropriate interventions are applied, ultimately reducing the illness burden of psychosis on the affected individuals and the healthcare system and maximizing outcomes for the individual.

1.3 Electroencephalography and Event-Related Potentials

Electroencephalography (EEG) is being investigated as a potential tool that could be used for the identification of individuals who are at-risk for psychosis development. EEG-derived event-related potentials (ERPs) are a direct and objective measure of neuronal functioning (Nunez et al., 2006). There are two main reasons why ERPs are advantageous when examining neuronal activity. First, EEG has a better temporal resolution, reporting on a millisecond by millisecond basis, compared to a second-by-second basis with other imaging techniques like functional magnetic resonance imaging (fMRI; Knappenman & Luck, 2012). Second, ERPs can provide insight into cognitive mechanisms before the presence (or even in the absence) of an overt behavioral response (van der Stelt & Belger, 2007). This makes ERPs a valuable tool for capturing the neuronal mechanisms of sensory processing in clinical populations such as individuals with psychosis.

1.3.1 The Mismatch Negativity and Theories of Generation

The mismatch negativity (MMN) is an ERP with negative polarity (i.e. an ERP that displays a negative microvoltage over the region of interest following the relevant stimuli) that occurs in the frontotemporal regions approximately 100-250 milliseconds following a detectable change in the auditory environment (Luck, 2014; Näätänen, 2003). The MMN can be conceptualized as a general indicator of auditory cortex function (Näätänen et al., 2007). Originally, MMN generation was believed to be dependent on the ability of the individual to perceive a frequent auditory stimuli and hold a template of that stimuli in sensory memory. The

MMN was hypothesized to be elicited when a new incoming auditory stimulus did not match the held memory of the previous sounds (Näätänen, 1990). Evidence that supported this theory involved the fact that the MMN is only generated when the deviant tone is played no more than 15 seconds following a standard tone (Cowan et al., 1993), suggesting the presentation of the standard tone was being held in sensory memory for that time. However, it was discovered that when engaged in a separate working memory task, there were no alterations to the MMN (Berti & Schröger, 2003), challenging this hypothesis.

The current dominant theory of how the MMN is elicited is the Predictive Coding Model. This model posits that based on the recently presented sound stimuli, the auditory system forms a prediction about the characteristics of the subsequent sound and an MMN is elicited when the next incoming stimulus does not match that prediction (Winkler, 2008). This theory is supported by the fact that the MMN amplitudes following a deviant stimulus are larger after multiple presentations of the standard stimulus (Todd et al., 2014). It is also supported by the fact that an MMN can be elicited by the absence of sound (Rudolph et al., 2015; Salisbury, 2012), suggesting it is the violation of a prediction, not the mismatch between an incoming sound and a memory trace, that elicits the MMN.

Although some studies have reported attentional allocation to the incoming stimulus can alter MMN amplitude (Sussman et al., 1998; Trejo et al., 1995), other studies have reported no effects of attention on MMN (Michie, 2001; Näätänen et al., 1993). Ultimately, it is widely accepted that MMN generation is not dependent on attentional processes, but may be suppressed or attenuated in the presence of highly focused auditory attention elsewhere (Woldorff et al., 1991). This independence of attentional processes allows the MMN to be generated in the absence of overt attention, making it particularly valuable when examining clinical populations

where deficits in attention and motivation may confound results on behavioural measures, such as in individuals with psychosis.

On a cellular level, there is critical involvement and dependence of MMN generation on N-methyl-D-aspartate (NMDA) receptors, which links this response to the glutamatergic system. The administration of both competitive and non-competitive NMDA receptor antagonists stops the generation of the MMN (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000). Further, considering glutamate (a primary excitatory neurotransmitter in the brain) binds to NMDA receptors, we can assume that MMN generation is closely associated with the glutamatergic system in the brain. Glutamate alterations have been robustly reported in chronic schizophrenia across multiple areas of the cortex (reviewed in Marsman et al., 2013; Merritt et al., 2016). In some cases, EPP samples also show these alterations (Bartolomeo et al., 2019; reviewed in Bissonnette et al., 2022; Nakahara et al., 2021). In CHR samples glutamate abnormalities have been reported in the frontal regions, and the thalamus, these alterations were related to the transition to psychosis in two studies (reviewed in Treen et al., 2016; Wenneberg et al., 2020). Although there are existing reports of no glutamate abnormalities in this population in the temporal (Wood et al., 2010), and frontal regions (Egerton et al., 2014; Natsubori et al., 2014), this evidence highlights the potential for MMN alterations in at-risk populations. This, along with the evidence that the MMN can be elicited in the absence of overt attention and therefore would not be confounded by attention and/or motivation deficits, makes the MMN response a hopeful candidate for a marker of illness vulnerability.

1.3.2 Paradigms Used to Elicit the Simple MMN

There have been multiple paradigms used to elicit the MMN experimentally. The oldest and most commonly used is the traditional oddball paradigm where a deviant tone (which is

identical to the standard tones in all physical attributes except one, typically in either duration or frequency) is presented between a random number of standard tones (Naatanen et al., 2004). The response for the standard tone is subtracted from the response for the deviant, and what remains is the true MMN in response to the deviant. The 'optimal' multi-feature MMN paradigm is similar to the oddball but it employs five deviant tone types (duration, frequency, intensity, location, and gap) and presents a deviant tone in between each standard tone (Naatanen et al., 2004). This paradigm is beneficial as it allows us to measure the MMN in response to several auditory attributes in the same amount of time as the oddball paradigm and derives a more comprehensive profile of auditory processing deficits. This is important considering the primary auditory cortex shows different patterns of activation depending on changes to different features of auditory stimuli (Kropotov et al., 2000; Levainen et al., 1993). This 'optimal' multi-feature MMN paradigm has been successful in detecting auditory processing deficits in multiple clinical populations (Bissonnette et al., 2020; Chang et al., 2015; Fisher et al., 2011).

1.4 Alterations to the MMN in Psychosis

1.4.1 MMN in Chronic Schizophrenia

Shelley et al. (1991) were the first to report a reduced MMN amplitude in chronic schizophrenia following a duration deviant. In the time since, this finding has been extensively replicated (Baldeweg et al., 2002, 2004; Bodatsch et al., 2011; Catts et al., 1995; Fisher et al., 2012; Javitt, 1995; Kaur et al., 2012; Light & Braff, 2005; Michie, 2001; Nagai et al., 2013; Umbricht et al., 2003). Multiple studies have found significant correlations between duration MMN amplitudes and longer illness duration (Baldeweg et al., 2002; Umbricht & Krljes, 2005), increased negative psychosis symptoms (Catts et al., 1995; Fisher et al., 2012), increased positive psychosis symptoms and auditory hallucinations (Fisher et al., 2012; Youn et al., 2003), and

more severe cognitive symptoms like impaired working memory and verbal fluency (Baldeweg et al., 2004; Light & Braff, 2005). Impaired daily functioning is also related to this deficit in chronic schizophrenia (Light & Braff, 2005; Rasser et al., 2011).

The effects of antipsychotic medication status on the MMN response have also been extensively evaluated in a chronic sample. Evidence from preclinical studies has been contradictory. It has simultaneously been reported that the chronic administration of antipsychotic medication increases NMDA receptor binding (Schmitt et al., 2003), and decreases NMDA receptor function in the animal cortex (Krzystanek & Pałasz, 2019). We know that antipsychotic medications typically do not directly target the glutamatergic NMDA receptors that underlie MMN generation, but rather act on the dopaminergic system in the cortex (Amato et al., 2018; Seeman, 2004). However, an ameliorated MMN amplitude following antipsychotic treatment (4 weeks of aripiprazole) has been reported in one sample (Zhou et al., 2013). Still, the majority of the evidence suggests a reduced duration MMN occurs regardless of medication status, as it has been seen in multiple fully medicated chronic samples (Catts et al., 1995; Liu et al., 2022; Michie, 2001). Further, two studies have administered six or more weeks of antipsychotic medication (olanzapine and clozapine) and reported no effects of these medications on the MMN response despite a significant improvement in psychosis symptoms (Korostenskaja et al., 2005; Umbricht et al., 1998).

It is possible that the amelioration of the MMN response following a course of antipsychotic treatment that has been reported once (Zhou et al., 2013) is due to the indirect impact of these drugs through interactions between the dopaminergic and glutamatergic systems and/or by improving connectivity and neuronal functioning throughout the cortex (Korostenskaja et al., 2007). It should be noted that while Zhou and colleagues (2013) did report a significant

improvement in the MMN response following antipsychotic treatment, the post-treatment MMN amplitudes were still significantly lower than the amplitudes of the healthy controls, suggesting that even though there were improvements, the response was not completely normalized by the medication. This, along with the multitude of reports of reduced MMN amplitudes in fully medicated samples, as well as the two reports of an absence of an effect of antipsychotic medication on the MMN response (Korostenskaja et al., 2005; Umbricht et al., 1998) suggest antipsychotic medication largely does not affect preattentional aspects of sensory processing represented by the MMN response.

Following tones that deviate in frequency, MMN reductions in chronic schizophrenia have also been reported (Hirayasu et al., 1998; Schall et al., 1999; Umbricht et al., 1999, 2003; Umbricht & Krljes, 2005). Additionally, Schall et al. (1999) reported a relationship between increased positive symptoms (specifically, auditory hallucinations) and lower frequency MMN amplitudes in the left hemisphere. However, unlike the duration deviant, there are significant conflicting reports of no frequency MMN alterations in this population (Bodatsch et al., 2011; Korostenskaja et al., 2005; Mondragón-Maya et al., 2013; Nagai et al., 2013).

Less extensively researched in chronic schizophrenia is the MMN in response to intensity, gap, and location deviants. Fisher et al. (2012) employed the 'optimal' multi-feature MMN paradigm and found reduced MMN amplitudes following location and gap deviants in a sample of individuals with chronic schizophrenia. Interestingly, they also reported a significant correlation between a reduced gap MMN response and frequency of auditory hallucinations, as well as a reduced location MMN and perceived location of auditory hallucinations (where reduced amplitudes were related to perceptions of hallucinations originating from outside the head rather than inside; Fisher et al., 2012).

1.4.2 MMN in Early Phase Psychosis

Reduced duration MMN amplitudes in EPP compared to a healthy population have been reported and replicated (Atkinson et al., 2012; Hermens et al., 2010; Kaur et al., 2012; Oades et al., 2006; Solís-Vivanco et al., 2014; Todd et al., 2008). There is also one report of no alterations to MMN amplitudes following a duration deviant in a sample of medicated patients with relatively low symptom severity indexed by an average PANSS score of 26 (Fisher et al., 2018), and one report of a trend towards reduced duration MMN amplitudes that did not reach significance (Umbricht et al., 2006). A recent meta-analysis of the duration MMN response in FEP found a moderate effect size of duration MMN reduction (Erickson et al., 2016). These reported deficits in duration MMN amplitudes seem to be related to psychosis symptom severity in some studies (Oades et al., 2006), and not in others (Atkinson et al., 2012; Hay et al., 2015; Kaur et al., 2012; Solís-Vivanco et al., 2014; Todd et al., 2008). Where reported, it seems as though increased negative symptoms of anergia and positive symptoms of hallucinations are related to a greater MMN deficit (Oades et al., 2006). However, the majority of studies examining the MMN in response to duration deviants fail to find any significant correlations with psychosis symptomology in the early phase of the illness. This duration MMN reduction is related to cognitive impairments in this early presentation of the illness (Hermens et al., 2010; Kaur et al., 2012). Kaur and colleagues (2012) found that reduced MMN amplitudes in response to duration deviants were related to worse performance on tasks that probed the cognitive domains of verbal learning, attentional switching, and mental control (Kaur et al., 2012). Further, Hermens and colleagues (2010) showed that a duration MMN reduction was related to slower processing speed in FEP (Hermens et al., 2010). Unlike the duration MMN reduction viewed in

the chronic presentation of the illness, within the early phase it does not appear as though a duration MMN reduction is related to measures of daily functioning (Hermens et al., 2010).

A reduced MMN in response to frequency deviants has also been reported in EPP (Hay et al., 2015; Oknina et al., 2005; Umbricht et al., 2006). Two studies that examined an EPP sample concurrently with a chronic SZ sample showed that frequency MMN amplitudes were intermediate between those of controls and chronic presentations of the illness (Oknina et al., 2005; Umbricht et al., 2006). No significant correlations between positive or negative psychosis symptoms, cognitive symptoms, or daily functioning and frequency MMN amplitudes in this population have been reported. Interestingly, there is evidence to suggest low premorbid education may be related to a reduction in frequency MMN. Umbricht and colleagues (2006) originally found no difference in frequency MMN amplitudes between an FEP group and controls, but they then divided their FEP sample into those with low and high pre-morbid education levels. Those with low levels of pre-morbid education did have significantly lower MMN amplitudes in response to frequency deviants (Umbricht et al., 2006).

Nonetheless, the majority of reports show no differences in MMN amplitudes to frequency deviants between EPP and healthy controls (Devrim-Üçok et al., 2008; Fisher et al., 2018; Salisbury et al., 2002; Todd et al., 2008). This is reflected in the meta-analysis that found no effect size for a frequency MMN reduction in EPP (*Cohen's d* < 0.04) and suggests frequency MMN reductions likely occur with chronicity and are not present at early presentations of the illness (Haigh et al., 2017). Interestingly, Devrim-Üçok and colleagues (2008) found no deficits in an FEP sample while they were acutely ill and medication naïve, but in a post-acute phase following antipsychotic medication administration deficits in frequency MMN amplitudes

appeared. Their work supported the hypothesis that the frequency MMN alteration is present with illness chronicity (Devrim-Üçok et al., 2008).

Three studies have examined the MMN in response to intensity deviants to date in EPP. Two of them found reduced amplitudes in patients compared to controls (Hay et al., 2015; Todd et al., 2008), and one found no significant differences (Fisher et al., 2018). None of these three studies found any correlations between intensity MMN amplitudes and psychosis symptoms. Regarding the remaining two deviant tone types included in the optimal multi-feature MMN paradigm (gap and location), to the best of our knowledge, there has only been one study employing this paradigm in an EPP sample to date. They found no significant differences between patients and controls nor any correlations with psychosis symptom scale scores (Fisher et al., 2018). Needless to say, the deviant tone types of intensity, location, and gap have not been studied extensively in this population and therefore require further investigation.

1.4.3 MMN in High-Risk Populations

Although frequency MMN has shown no difference in a CHR population compared to controls (Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005), reduced duration MMN in CHR individuals has been extensively reported (Atkinson et al., 2012; Higuchi et al., 2013; Hsieh et al., 2012; Solís-Vivanco et al., 2014). Studies that used a longitudinal design to follow CHR individuals and see if they do convert to psychosis have found converters had a reduced duration MMN, while non-converters showed similar duration MMN amplitudes to controls (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2013; Shaikh et al., 2012). One study found no significant difference in duration MMN amplitudes between CHR, EPP, and healthy controls, however, the EPP and healthy control groups were significantly different from each other, and the CHR group was in-between those two means (Brockhaus-Dumke et al., 2005). These

findings could indicate that duration MMN is reduced in some but not all CHR individuals, and may be a potential predictor of conversion to psychosis

Studies examining the MMN in first-degree family members of those with psychosis (GHR) have been largely inconsistent. Some studies have reported reduced MMN following frequency (Jessen et al., 2001) and duration deviants (Michie et al., 2002; Şevik et al., 2011). However, a relatively equal amount report no difference between GHR individuals and healthy controls (Ahveninen et al., 2006; Bramon, 2004; Magno et al., 2008). This suggests duration nor frequency MMNs are good endophenotypic markers of psychosis, but rather a result of illness progression. Hall and colleagues (2007) supported this view by reporting that duration MMN has only weak familial underpinnings compared to other ERPs.

1.4.4 Summary of MMN Alterations Across Illness Phase

Ultimately, the MMN (particularly in response to duration and frequency deviants) has been extensively studied in chronic samples. When reviewing the body of ERP work in this area, previous reports seem to suggest the MMN in response to duration deviants is the most consistently altered compared to any other deviant tone type (i.e. frequency, intensity, gap, location). Considering the MMN in response to duration deviants is consistently altered in chronic schizophrenia, it has been proposed as a biomarker for psychosis risk. However, if the duration MMN was truly a good marker for the development of psychosis, then there would be robust findings of reductions in FEP and EPP samples. A meta-analysis of the literature reported a weak to moderate effect size (Hedges' g = 0.42) of MMN reduction in early presentations of psychosis (Erickson et al., 2016).

This suggests that although there are clearly some alterations to early sensory processing in these populations, the current method of eliciting the MMN is not giving us a reliable measure

of these deficits in all phases of illness. Additionally, the progressive reduction of the MMN has been reported over multiple time points throughout illness progression (Devrim-Üçok et al., 2008; Salisbury et al., 2007), and is related to worse psychosis symptoms (Catts et al., 1995; Fisher et al., 2012; Oades et al., 2006; Salisbury et al., 2002; Youn et al., 2003), suggesting the MMN response may be a better representative of a state marker of illness rather than a trait marker of illness vulnerability (Shinozaki et al., 2002). Therefore, the search for a valid marker of psychosis risk within the auditory processing system continues, and the exploration of other ways to probe these early sensory processes that are better suited to capture subtle changes in cortical function have become a research interest.

1.5 Introducing the Complex Mismatch Negativity

Recently, the utilization of MMN paradigms that require more complex computational resources on the cortical level has been of interest. The underlying theory behind the development of these new MMN paradigms is that heterogeneity of the literature on MMN alterations in EPP populations exists in part because auditory processing deficits in these populations are more-subtle than those of more advanced presentations of psychosis. Specifically, the neuronal computations required to process a deviant tone that only varies from a standard in one singular physical attribute (to elicit an MMN) are much simpler than the computations needed to process a deviant that varies from a standard in multiple physical dimensions, or that violates an established pattern. Therefore, paradigms that require this more complex MMN computation are considered to elicit a complex MMN (cMMN). It is hypothesized that cMMN generation relies on higher-order cognitive processing that employs the frontal cortex as well as the primary auditory cortex, while the MMN generation relies simply on the primary auditory cortex (Avissar et al., 2018). Due to the computational complexity and

demand on higher-order processing the cMMN generation requires, it is hypothesized that the cMMN will deteriorate earlier in illness progression than the MMN response, and therefore will be a more sensitive marker of psychosis vulnerability than an MMN response.

Multiple types of cMMN paradigms have been explored to date. First, complex sensory MMN paradigms (also referred to as double deviant paradigms) utilize deviant tones that vary from the standard in more than one physical attribute. In the majority of these paradigms, the deviant tone varies from the standard in duration and frequency. Hong et al. (2012) used this paradigm in a sample of individuals with chronic schizophrenia and found no differences between patients and controls (Hong et al., 2012). However, Perez et al. (2014) and Hay et al. (2015) reported reduced cMMN amplitudes were reduced in EPP samples (Hay et al., 2015; Perez et al., 2014). Furthermore, cMMN responses elicited by utilizing this double deviant paradigm were able to predict conversion to psychosis in a CHR sample (Perez et al., 2014).

Alternative paradigms to elicit the cMMN include complex pattern paradigms. These paradigms establish patterns of sensory stimuli and elicit a cMMN when a violation to the pattern occurs rather than changing a physical attribute of the deviant tone. The most robustly reported of these paradigms is the missing stimulus or omission cMMN paradigm. This paradigm is based on the Gestalt principle of proximity and presents a string of standard tones followed by another string of tones that is missing one of the tones. A prediction that the second string will be the same as the first is made and the cMMN is elicited when that prediction is violated by the absence of a tone. No alterations to cMMN amplitudes in a chronic patient group have been reported using this paradigm in one study (Hayakawa et al., 2013), but other studies report reductions in chronic schizophrenia samples (Salisbury & McCathern, 2016), as well as in EPP (Rudolph et al., 2015).

Additional complex pattern paradigms that have been developed include those that present an extra tone to violate a pattern (Haigh et al., 2016; Salisbury et al., 2020), those that alter the interstimulus interval between tones (Davalos et al., 2003, 2005; Todd, 2006), and those alternate between two tones and then create a pattern deviation by repeating a tone (Ells et al., 2018). Although some of these examined paradigms have been successful in observing differences in chronic samples (Davalos et al., 2003, 2005; Todd, 2006) and in EPP (Haigh et al., 2016; Salisbury et al., 2020), a recent meta-analysis determined that the effect sizes derived from these cMMN studies were comparable to those reported from traditional MMN paradigms (Avissar et al., 2018). This suggests one of two things; first, that the cMMN response is no more sensitive than the traditional MMN response when it comes to detecting differences in auditory processing abilities, or that the optimal method of eliciting the cMMN to detect robust changes across the illness phases in psychosis has not yet been found. To further explore the latter possibility, new cMMN paradigms are currently being developed by Dr. Dean Salisbury and colleagues at the University of Pittsburgh.

One of the prominent new paradigms is a complex pattern paradigm that establishes two pattern rules simultaneously compared to previous complex pattern paradigms that only establish one pattern. This new paradigm, hereby referred to as the dual rule complex paradigm, breaks two pattern rules simultaneously by establishing a pattern of low-frequency tones played to the left ear, and high-frequency tones played to the right. The deviant tone that elicits the MMN is a repeated tone in the pattern, thus breaking both the right/left alternating pattern and the high/low-frequency pattern (see Figure 2). Adding an additional pattern rule to a cMMN paradigm requires an increased computational demand on the cortex to hold two pattern rules in sensory memory, and then detect the deviation from those two rules. This increased demand on the

cortex was therefore hypothesized to be advantageous in detecting more subtle deficits that occur early on in illness progression.

1.6 The Current Study

This study addresses the lack of appropriate measures to elicit the cMMN in the literature by being the first to explore the cMMN elicited by the novel dual rule cMMN paradigm. Assessing this response in a sample of individuals in the early phase of illness would be one of the first steps to determining its potential as a utilizable marker for psychosis vulnerability. The development of a more specific and sensitive tool to determine who is at high risk for developing psychosis than simply the presence of prodromal symptoms is crucial. One such tool could be used to determine who would benefit the most from early interventions to prevent the development of the illness.

1.6.1 Aims and Objectives

The primary aim of the current study was to provide novel insight into the cMMN elicited by the newly developed dual rule MMN paradigm in a sample of individuals within the early phase of psychosis compared to healthy controls. A secondary aim was to add to the existing body of literature on simple MMN alterations in early phase psychosis following duration, frequency, intensity, location, and gap deviants using the 'optimal' multi-feature MMN paradigm. Third, an additional purpose of including the optimal multi-feature MMN paradigm was to allow us to compare the presence and magnitude of the effect sizes of a dual rule cMMN reduction to the classic MMN reduction and provide insight into whether the new dual rule cMMN paradigm does indeed show larger and potentially more robust deficits in psychosis than the classic MMN paradigm. Finally, we also aimed to investigate the relationships between a

wide range of psychosis symptoms, social and occupational functioning, and past adverse events in the EPP group and the MMN/cMMN amplitudes and latencies.

1.6.2 Hypotheses

First, we hypothesized that the cMMN amplitudes derived from the novel Dual Rule paradigm in the EPP group would be reduced compared to the healthy control group in accordance with previous findings (Avissar et al., 2018; Rudolph et al., 2015; Salisbury et al., 2020). Second, we hypothesized that MMN amplitudes following all five deviant tone types from the 'optimal' multi-feature MMN paradigm would not be altered in the EPP group to reflect the inconsistency seen in the literature (Erickson et al., 2016). Third, we hypothesized that the observed effect sizes from the dual rule cMMN paradigm would be larger than those observed in the optimal multi-feature MMN paradigm because we believed the Dual Rule paradigm would be a more sensitive measure of reductions to the auditory processing system due to its increased computational complexity in breaking two abstract pattern rules simultaneously.

Finally, regarding the aim of investigating the relationships between a wide range of psychosis symptoms, social and occupational functioning, and past adverse events in the EPP group, we hypothesized that reduced MMN amplitudes from the optimal multi-feature paradigm would be related to more severe psychosis symptoms in the EPP group as we believe a reduced MMN is more representative of a state marker of illness, rather than a trait marker of vulnerability. We also hypothesized that both more severe psychosis symptoms and measures of functioning would be related to reduced cMMN amplitudes elicited by the dual rule paradigm in accordance with previous findings examining the cMMN response using an alternative cMMN paradigm (Ells et al., 2018). Finally, the investigation of the prevalence of past adverse life experiences and their relationship to neurophysiological variables was exploratory.

Chapter 2: Methods

2.1 Participants

The early phase psychosis (EPP) group was recruited through the Nova Scotia Early Psychosis Program (NSEPP). We recruited a sample of 15 individuals (10 males, 5 females) between the ages of 20-26 (M_{age} = 22.9, SD_{age} = 2.2) who were within the first five years of admission to the Nova Scotia Early Psychosis Program (NSEPP). The specific diagnoses of the EPP group were as follows: seven individuals with schizophrenia, three individuals with unspecified schizophrenia spectrum disorder, two individuals with schizoaffective disorder, one individual with substance-induced psychosis, one individual with schizophreniform disorder, and one individual with borderline personality disorder.

Healthy controls (HC) were recruited from the general population through electronic (e.g. Facebook Marketplace, Kijiji, Craigslist) and paper advertisements (placed at Mount Saint Vincent University, Dalhousie University, and the QEII Health Sciences Centre; see Appendix A) and through word of mouth (via snowball effect). We recruited 20 healthy controls (5 males, 15 females) between the ages of 18-26 (M_{age} = 22.8, SD_{age} = 2.4). HCs had negative self-reported histories of psychiatric and neurological illness, as well as no first-degree relatives with psychosis to protect against any potential alterations to the MMN response in unaffected immediate family members that have been previously reported (Michie et al., 2002).

Participants were excluded if they met any of the following criteria: self-reported co-morbid DSM-5 Axis I disorder (or current self-reported disorder in HC group); self-reported current DSM-5 substance use disorder; a history of significant head injury resulting in loss of consciousness within the past year; diagnosis of epilepsy or any other neurologic disorder; electro-convulsive therapy (ECT) treatment within the previous year; significant cardiac illness;

chronic medical illness requiring regular medication; extrapyramidal symptoms (EPS) resulting in movement disorders; abnormal audiometric assessment.

All participants were required to be right-handed, as determined by a handedness inventory to ensure source localization during analysis (Oldfield, 1971). Participants were required to have normal or corrected-to-normal vision and normal hearing, as determined by self-report, to ensure these were not confounds to the study. Finally, it was mandatory that participants could read and understand both spoken and written English for the informed consent procedures and self-report measures. All procedures described were approved by the Nova Scotia Health Authority Research Ethics Board (file #1024402), and the IWK Research Ethics Board (file #1026464).

2.2 Questionnaires

2.2.1 Global Assessment of Functioning Scale

The Global Assessment of Functioning Scale (GAFS) rates the social, occupational, and psychological functioning of adults, and has shown to have adequate reliability as well as validity (Hall, 1995; Startup et al., 2002). GAFS scores are derived following an unstructured interview with a member of the research team with appropriate clinical training. The GAFS is scored out of 100, and a higher score indicates better overall functioning of the individual (see Appendix B).

2.2.2 Social and Occupational Functioning Assessment Scale

The Social and Occupational Functioning Assessment Scale (SOFAS) is a subjective measure that is derived through an unstructured interview with a trained member of the research team (see Appendix C). SOFAS scores are a composite of adaptive living skills, social appropriateness, and interpersonal skills subjectively rated by a member of the research team with appropriate clinical training. Impairment in one or more of these areas is only counted

towards the final SOFAS score if is it not the effect of a lack of opportunity or environmental constraints. SOFAS scores range from 1-100, and a higher score represents better social and occupational functioning. The SOFAs is a reliable measure of trait functioning in the general population that is separate from the direct impact of psychiatric symptoms (Saraswat et al., 2006).

2.2.3 Scale of Prodromal Symptoms

The Scale of Prodromal Symptoms (SOPS) is a 19-item scale designed to assess prodromal symptoms of psychosis in a high-risk population (Miller et al., 1999). This scale is modeled off of the Positive and Negative Syndrome Scale (PANSS) but is adapted to include an increased breadth of symptoms to encompass symptoms of sub-clinical severity (see Appendix D). The current study utilized two SOPS subscales of positive and negative symptoms. The positive subscale consists of five items (P1: unusual thought content/delusional ideas; P2: suspiciousness/persecutory ideas; P3: grandiose ideas; P4: perceptual abnormalities/hallucinations; P5: disorganized communication), and the negative subscale consists of six items (N1: social anhedonia; N2: avolition; N3: expression of emotion; N4: experience of emotion and self; N5: ideational richness; N6: occupational functioning). This measure is a reliable and valid measure of psychosis symptoms in high-risk populations (Miller et al., 2003). Additionally, SOPS scores are highly correlated with other measures of psychosis symptoms such as the PANSS and the Scales for the Assessment of Negative and Positive Symptoms (SANS/SAPS) (Fulford et al., 2014; Tso et al., 2017). The SOPS has previously been employed in an EPP sample to assess the degree of psychosis symptoms (Tso et al., 2017).

2.2.4 Psychotic Symptoms Rating Scales

The Psychotic Symptoms Rating Scales (PSYRATS) was used to assess auditory hallucinations in our EPP group (see Appendix E). The PSYRATS is a semi-structured interview designed to assess the subjective characteristics of auditory hallucinations in schizophrenia. The PSYRATS has also been validated in a sample of individuals in the early phase of psychosis and complements additional measures of psychosis symptomology by probing a detailed profile of auditory hallucination dimensions (Drake et al., 2007). The PSYRATS can be divided into four subscales including distress, frequency, attribution, and loudness of auditory hallucinations (Woodward et al., 2014).

2.2.5 Trauma and Life Events Checklist

The Trauma and Life Events (TALE) checklist was developed as a brief screening tool for traumatic or aversive life events in psychosis patients (see Appendix F). The TALE is a 21-item self-report questionnaire that assessed the occurrence and frequency of a wide variety of psychologically and physically threatening events including psychosis-related traumas. The TALE measure shows acceptable reliability and validity as a trauma measure in psychosis (Carr et al., 2018).

2.3 Procedure

The first step in participation was a brief screening questionnaire that was completed over the phone to determine the eligibility of the volunteer (see Appendix G). At the same time as the screening, demographic variables of age, sex, level of education, and self-reported weekly average alcohol and cannabis consumption were obtained. If the volunteer met all inclusion criteria and was eligible to participate, they scheduled a time to come into the lab (at the Abbie J. Lane building in Halifax, Nova Scotia) for one session. All sessions started were completed

between the hours of 12:00 pm to 3:00 pm to account for circadian fluctuations in alertness and EEG patterns throughout the day (Hines, 2004). Participants were required to abstain from alcohol, cannabis, and illicit substances from midnight the night before the session. Participants in the EPP group were instructed to take their medications (including antipsychotic and adjunct drugs) as usual. Upon arrival to the session, verbal confirmation of abstinence was obtained from each participant.

Once arrived at the lab, the participant read the written informed consent document. Following informed consent procedures, the participant completed all relevant questionnaires for their experimental group. HCs completed the TALES and SOFAS measures. The EPP group completed the TALES, SOFAS, GAFS, SOPS, and PSYRATS measures. Following the completion of the questionnaires, EEG electrodes were applied. Participants were instructed to watch a silent film while a battery of auditory MMN paradigms was presented that included the 'optimal' multi-feature MMN paradigm followed by the dual rule MMN paradigm. At the end of each session, a compensation of $25.00 was given to offset the cost of transportation and to reimburse participants for their time.

2.4 'Optimal' Multi-feature Paradigm Parameters

Within this paradigm, every second tone is standard and every other tone is one of five deviants. Standard stimuli are tones of 75 ms duration (including 5 ms rise and fall). The sound pressure level of the standard tones is 70 dB. Except where stated, the deviants are identical to the standards. The deviants vary from the standard tone in either pitch, duration, intensity, perceived location, or continuity (whether there is a gap in the middle of the tone). Half of the frequency deviants are 10% higher (composed of 550, 1100, and 1650 Hz partials) while the other half are 10% lower (450, 900, and 1350 Hz partials). Half of the intensity deviants are at 60

dB while the other half are at 80 dB. The perceived difference between the standard tone and the location deviant is approximately 90°; the chance in the perceived location of sound origin is obtained by creating a time difference of 800 μs for half of the location deviants to the right channel and half of the deviants to the left. The duration deviant is shorter than the standard (25 ms), while the gap deviant is created by removing 7 ms (including 1 ms rise and fall) from the middle of the standard stimulus. The stimuli were presented binaurally in three 5-minute intervals and participants were given short breaks (1-2 minutes) between each block. See figure 1 for a visual representation of the optimal multi-feature MMN paradigm.

2.5 Dual Rule Paradigm Parameters

The novel dual rule MMN paradigm consists of tones that alternate between presentation to the left and right ear, as well as alternate between high and low frequency. The standard trial pattern consists of the low frequency tone played to the left ear, then the high frequency tone played to the right ear. Deviant trials consist of two presentations of the standard pattern occur, followed by the low frequency tone played to the left ear twice (i.e. a repetition of the first tone in the standard pattern, or a tone that fails to switch both frequency and location thus breaking the two established patterns of left/right and high/low frequency). Marked deviant tones were the second presentation of the low frequency tone to the left ear in this deviant trial. High-frequency tones were composed of 1200 Hz partials delivered to the right ear. Low-frequency tones were composed of 1000 Hz partials delivered to the left ear. Deviant trials were situated amongst standard trials in a randomized manner within the paradigm, but each participant received identical versions of the paradigm. Both tones were 75ms in length with 5ms rise and fall. The interstimulus interval was 330ms. Standard trials were presented six times before a deviant trial resulting in deviant tones contributing to 11% of the presented stimuli. The stimuli were

presented binaurally through headphones at an intensity of 75 dB SPL in one 8-minute interval. See figure 2 for a visual representation of the dual rule cMMN paradigm.

2.6 EEG Recording Parameters

EEG recording and computation was digitally sampled at 500 Hz from an active electrode cap with Ag+/Ag+-Cl- electrodes at 64 scalp sites. Scalp sites were chosen according to the 10-10 system of electrode placement (See figure 3; Chatrian et al., 1985). Relevant data was collected from electrode placements at two midline sites (frontal [Fz], central [Cz]), two right hemisphere (frontal [F4], central [C4]) electrode sites, and two left hemisphere (frontal [F3], central [C3]) electrode sites. Electrodes were also placed bilaterally on both mastoids. Recordings of vertical electrooculogram activity was taken from Fp1/Fp2. All electrode impedances were kept under 10 kΩ at the time of recording. Electrical activity was recorded using an ActiCHamp (Brain Products, Gilching, NE) with a bandpass filter of DC-250Hz, and stored on a hard disk for later off-line analysis.

2.7 MMN Computation

Offline EEG data processing included first applying IIR filters from 0.1-20 Hz with a notch filter at 60 Hz to all electrode sites except Fp1 and Fp2, which were filtered from 0.1-3 Hz to enhance electrooculogram activity at these sites to be used for later ocular correction. Then, segmentation relative to each deviant tone was completed including 100 ms before and 700 ms after each tone. An ocular correction was then completed using the filtered Fp1/Fp2 channels as reference followed by a baseline correction starting 100 ms pre-stimulus. Artifact rejection was done for any epoch exceeding 50 μV. Finally, averages were taken for each deviant type within each participant.

The MMN difference waveforms were derived by digital point-by-point subtraction of the values from the standard stimulus presentations from those elicited by the presentation of the deviant stimuli. MMN peaks were assessed by quantifying peak negative amplitudes (relative to average pre-stimulus baseline activity) within an analysis window based on visual inspection. The output was the average electrical activity within eight voltage points to the left and right of the peak amplitude.

2.8 Statistical Analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk NY). Demographic variables of age, level of education, and weekly self-reported alcohol and cannabis use as well as total scores on the SOFAS and TALES measures were compared between groups using independent samples t-tests where equal variances were assumed. The variable of sex was compared between groups using a chi-square test of independence. MMN amplitudes for each deviant type (duration, frequency, intensity, gap, and location), and cMMN amplitudes from the dual rule paradigm were subjected to separate general linear model (GLM) mixed measures analyses of variance (ANOVA). Each ANOVA had the between-subjects factor of group (2 levels: HC, EPP) and two within-subject factors of frontality (2 levels: frontal, central) and laterality (3 levels: right, midline, left). This allowed us to examine MMN amplitude at regions, literalities, and single electrode sites (F3, Fz, F4, C3, Cz, C4) separately. Follow-up analyses of significant ($p < .05$; Bonferroni-corrected) main or interaction effects found in the ANOVAs were carried out with pairwise comparisons using separate (vs. pooled) error estimates.

Bi-variate (non-parametric) Spearman's rho correlations were carried out between the demographic variables of age, level of education, and weekly self-reported alcohol and cannabis

use, as well as total scores on the SOFAS and TALES in both EPP and HC groups separately. Moreover, GAF scores and psychosis symptom scale scores (SOPS and PSYRATS) were subjected to bi-variate Spearman's rho correlations with mean MMN amplitudes/latencies for each deviant type and cMMN amplitudes from the dual rule paradigm in the EPP group; correlations with all MMN amplitudes included sites Fz and Cz only, while only MMN latencies at Fz were included in analyses. The threshold for statistical significance was $p < .05$.

Chapter 3: Results

3.1 Optimal Multi-feature MMN Paradigm

Due to technical issues during recording, optimal multi-feature MMN data was discarded from two EPP participants (final n = 13; 5 females) as well as three HC participants (final n = 17; 12 females).

3.1.1 Group Demographic Variable Comparison

HC and EPP groups did not vary significantly in age, level of education, or weekly reported alcohol or cannabis consumption (see Table 1). The HC group had a higher percentage of females than males (71% female) compared to the EPP group which had a higher percentage of males than females (38% female), however, the proportion of male participants did not differ significantly by group (X^2 [1, N = 30] = 3.096, p = .078). Individuals in the EPP group reported significantly more adverse life events on the TALE questionnaire (t[28] = -3.735, p < .001), and also had significantly lower SOFAS scores (t[28] = 4.297, p < .001) than the HC group. The average SOPS scores for each subscale ranged from 0.7 to 2.3 (out of a possible 6). This indicates a mild symptom severity on average in our sample that aligns with an outpatient group. All average psychosis symptom scale scores for the EPP group are reported in table 2.

3.1.2 Duration MMN Amplitude

See figure 4 for the MMN response to duration deviants in the frontal region. There were no significant main effects of group or region. There was a main effect of site (F[2, 27] = 5.093, p = .010, g = 0.27), where the MMN amplitudes in response to duration deviants were significantly lower over the left hemisphere sites (M = -1.66μV, SD = 1.75μV) compared to midline sites (M = -2.19μV, SD = 2.21μV).

There were no significant group-by-site or group-by-region interactions. However, a planned pairwise comparison revealed a significant group-by-region-by site interaction where MMN amplitudes in response to duration deviants were lower in the EPP group (M = -0.95μV, SD = 1.28μV) compared to the HC group (M = -2.31μV, SD = 1.93μV) at electrode site F3 only (F[1, 28] = 4.859, p = .036, g = 0.82; see Table 3).

3.1.3 Frequency MMN Amplitude

See figure 5 for the MMN response to frequency deviants in the frontal region. There were no significant main effects of group, region, or site for MMN amplitudes in response to frequency deviants. Planned pairwise comparisons showed that there was a significant group-by-site interaction where MMN amplitudes in response to frequency deviants were higher in the HC group (M = -2.40μV, SD = 1.91μV) compared to the EPP group (M = -1.06μV, SD = 1.06μV) at electrode sites over the right-hemisphere (F[1, 28] = 4.339, p = .047, g = 0.87). Additionally, a significant group-by-region-by-site interaction revealed the HC group (M = -2.37μV, SD = 2.48μV) had higher MMN amplitudes in response to frequency deviants than the EPP group (M = -0.86μV, SD = 1.06μV) at electrode site C4 (F[1, 28] = 4.195, p = .050, g = 0.79; see Table 4).

3.1.4 Intensity MMN Amplitude

See figure 6 for the MMN response to intensity deviants in the frontal region. There were no significant main effects of group or region. There was a main effect of site where MMN amplitudes in response to intensity deviants were higher over both the midline sites (M = -1.77μV, SD = 1.61μV; F[2 , 27] = 4.329, p = .027, g = 0.27) as well as the right hemisphere sites (M = -1.72μV, SD = 1.58μV; F[2, 27] = 4.329, p = .027, g = 0.24) compared to the left hemisphere sites (M = -1.31μV, SD = 1.78μV). There were no significant interaction effects with group, region, or site for MMN amplitudes in response to intensity deviants (see Table 5).

3.1.5 Gap MMN Amplitude

See figure 7 for the MMN response to gap deviants in the frontal region. There were no main effects of group or site. There was a main effect of region ($F[1, 28] = 5.449$, $p = .027$, $g = 0.20$), where MMN amplitudes in response to a gap deviant were higher at the frontal region ($M = -2.11\mu V$, $SD = 1.56\mu V$) compared to the central region ($M = -1.75\mu V$, $SD = 1.99\mu V$). There were no significant interaction effects with group, region, or site for MMN amplitudes in response to gap deviants (see Table 6).

3.1.6 Location MMN Amplitude

See figure 8 for the MMN response to location deviants in the frontal region. There were no significant main effects of group, region, or site for MMN amplitudes in response to location deviants. There were also no significant interaction effects (see Table 7).

3.1.7 MMN Latencies

There were no significant differences between the EPP and HC groups in MMN latency to any deviant tone type (see Tables 3-7).

3.1.8 Correlations

More self-reported alcoholic drinks per week was related to lower MMN amplitudes in response to frequency deviants at Fz in the EPP group ($r = 0.665$, $p = .013$) as well as the HC group ($r = -0.690$, $p = .002$). Moreover, higher SOFAS and GAF scores were related to lower MMN amplitudes in response to location deviants at Cz ($r = 0.734$, $p = .004$) in the EPP group.

3.1.8.1 Positive Psychosis Symptoms. Longer MMN latencies in response to location deviants were related to higher PSYRATS total scores ($r = 0.685$, $p = .010$), as well as the PSYRATS frequency subscale ($r = 0.675$, $p = .011$) and the loudness subscale ($r = 0.636$, $p =$

.020). Further, the "perceptual abnormalities/hallucinations" (P4) subscale of the SOPS was also related to longer MMN latencies following location deviants (r = 0.667, p = .013).

There were also various significant correlations between increased MMN amplitudes in response to multiple deviant types and higher PSYRATS scores. PSYRATS total scores were related to higher MMN amplitudes in response to duration deviants at Cz (r = -0.582, p = .037). Higher scores on the distress subscale of the PSYRATS were related to increased MMN amplitudes in response to duration deviants at Cz (r = -0.702, p = .007) and Fz (r = -0.673, p = .012), gap deviants at Fz (r = -0.587, p = .035) and frequency deviants at Fz (r = -0.610, p = .027). There were no significant correlations found between MMN amplitudes to any deviant tone type and the frequency, attribution, or loudness subscales of the PSYRATS.

Higher scores on the "unusual thought content/delusional ideas" (P1) subscale of the SOPS were related to increased MMN amplitudes following the duration deviant at Cz (r = -0.601, p = .030), gap deviant at Fz (r = -0.558, p = .047), and location deviant at Cz (r = -0.590, p = .034). Higher scores on the "suspiciousness/persecutory ideas" (P2) subscale of the SOPS were related to increased MMN amplitudes following the frequency deviant at Fz (r = -0.670, p = .012). Higher scores on the "grandiose ideas" (P3) subscale of the SOPS were related to increased MMN amplitudes following gap deviants at Fz (r = -0.556, p = .049).

3.1.8.2 Negative Psychosis Symptoms. Higher scores on the "avolition" (N2) subscale of the SOPS were related to shorter MMN latencies in response to gap deviants (r = -0.555, p = .049).

Higher scores on the "social anhedonia" (N1) subscale of the SOPS were related to increased MMN amplitudes following duration deviants at Cz (r = -0.779, p = .002) and Fz (r = -0.790, p = .001; see Figure 9) and frequency deviants at Cz (r = -0.625, p = .022).

Higher scores on the "experience of emotions and self" (N4) were related to increased MMN amplitudes following the location deviant at Cz (r = -0.603, p = .029).

Finally, higher scores on the "occupational functioning" (N6) subscale of the SOPS were related to increased MMN amplitudes following the duration deviant at Cz (r = -0.627, p = .022), frequency deviants at Fz (Fz: r = -0.627, p = .022), and location deviants at Cz (r = -0.657, p = .015).

3.2 Dual Rule Complex MMN Paradigm

Due to technical issues during recording, dual rule cMMN data was discarded from one EPP participant (final n = 14; 5 females) as well as five HC participants (final n = 15; 11 females).

3.2.1 Group Demographic Variable Comparison

HC and EPP groups did not vary significantly in age, level of education, or weekly reported alcohol or cannabis consumption. The HC group had a higher percentage of females than males (73% female) compared to the EPP group which had a higher percentage of males than females (36% female). The proportion of male participants did significantly differ by group (X^2 [1, N = 29] = 4.144, p = .042). Individuals in the EPP group reported significantly more adverse life events on the TALE questionnaire (t[27] = -3.77, p < .001), and also had significantly lower SOFAS scores (t[27] = 4.23, p < .001) than the HC group (see Table 8). The average SOPS scores for each subscale ranged from 0.6 to 2.2 (out of a possible 6). This indicates a mild symptom severity on average in our sample that aligns with an outpatient group. All average psychosis symptom scale scores for the EPP group are reported in table 9.

3.2.2 Complex MMN Amplitude

There was a significant main effect of site where cMMN amplitudes were higher over midline sites (M = -3.15μV, SD = 3.12μV) compared to left hemisphere sites (M = -2.46μV, SD = 2.71μV) across both EPP and HC groups (F[2, 26], = 12.843, p = .003, g = 0.24). A planned pairwise comparison showed a significant group-by-region interaction were the HC group (M = -3.43μV, SD = 2.68μV) had higher cMMN amplitudes compared to the EPP group (M = -1.85μV, SD = 1.36μV) at the frontal region (F[1, 27] = 5.042, p = .033, g = 0.74) but this was not significant at the central region (p = .178). Further planned pairwise comparisons revealed significant group-by-region-by-site interactions where there were higher cMMN amplitudes in the HC group (M_{F4} = -3.45μV, SD_{F4} = 3.10μV; M_{Fz} = -3.91μV, SD_{Fz} = 2.57μV) compared to the EPP group (M_{F4} = -1.63μV, SD_{F4} = 1.21μV; M_{Fz} = -2.01μV, SD_{Fz} = 1.12μV) at F4 (F[1, 27] = 4.222, p = .050, g = 0.76) and Fz (F[1, 27] = 6.501, p = .017, g = 0.95) electrode sites (see Figure 10; Table 10).

3.2.3 Complex MMN Latency

There was no significant difference in cMMN latency between HC and EPP groups (see Table 10).

3.2.4 Early Phase Psychosis Group Correlations

In the EPP group, higher age was related to lower cMMN amplitudes at Cz (r = 0.584, p = .028). High self-reported weekly alcohol consumption was also related to lower cMMN amplitudes at Fz (r = 0.539, p = .047), and this was not significant in the HC group (r = -0.119, p = .674). Self-reported frequency of cannabis use, TALE and SOFAS scores were not significantly related to the cMMN response.

3.2.4.1 Positive Psychosis Symptoms. Increased auditory hallucinations as measured by the PSYRATS total scores were related to higher cMMN amplitudes at Fz (r = -0.632, p = .015; see Figure 11). When separated into sub-scales, there were significant correlations between increased cMMN amplitudes and increased scores on the distress subscale at Fz (r = -0.566, p = .035), the frequency subscale at Fz (r = -0.564, p = .036), and the loudness subscale at Fz (r = -0.547, p = .043). Positive psychosis symptoms measured by the SOPS were related to increased cMMN amplitudes as well. Specifically, higher scores on the "perceptual abnormalities/hallucinations" (P4) subscale were related to increased cMMN amplitudes at Fz (r = -0.582, p = .029).

3.2.4.2 Negative Psychosis Symptoms. There were no significant correlations between negative psychosis symptoms measured by the SOPS and cMMN amplitudes or latencies.

3.3 Hypotheses

Our first hypothesis that the cMMN amplitudes derived from the novel Dual Rule paradigm in the EPP group would be reduced compared to the healthy control group was supported. cMMN amplitudes were higher in the HC group (M_{F4} = -3.45μV, SD_{F4} = 3.10μV; M_{Fz} = -3.91μV, SD_{Fz} = 2.57μV) compared to the EPP group (M_{F4} = -1.63μV, SD_{F4} = 1.21μV; M_{Fz} = -2.01μV, SD_{Fz} = 1.12μV) at F4 (F[1, 27] = 4.222, p = .050, g = 0.77) and Fz (F[1, 27] = 6.501, p = .017, g = 0.96) electrode sites.

Our second hypothesis that MMN amplitudes following all five deviant tone types from the 'optimal' multi-feature MMN paradigm would not be altered in EPP was only partially supported. There were no significant differences in MMN amplitudes between groups following the intensity, gap, and location deviants. However, MMN amplitudes in response to duration deviants were lower in the EPP group (M = -0.95μV, SD = 1.28μV) compared to the HC group

(*M* = -2.31μV, *SD* = 1.93μV) at electrode site F3 only (F[1, 28] = 4.859, *p* = .036, *g* = 0.83). Also, the HC group (*M* = -2.37μV, *SD* = 2.48μV) had higher MMN amplitudes in response to frequency deviants than the EPP group (*M* = -0.86μV, *SD* = 1.06μV) at electrode site C4 (F[1, 28] = 4.195, *p* = .050, *g* = 0.79).

Our third hypothesis that the observed effect sizes from the dual rule cMMN paradigm would be larger than those observed in the optimal multi-feature MMN paradigm was also partially supported. The magnitude of the reduction for cMMN response from the dual rule paradigm was indeed larger (*g* = 0.95) than the magnitude of the reduction for the significantly reduced duration MMN amplitude reported (*g* = 0.82). It should be noted however, the confidence interval for this effect of a duration MMN amplitude deficit in EPP at F3 (CI [-1.52, -0.05]) did overlap with the confidence interval for the effect of a cMMN amplitude deficit in EPP (CI [-1.66, -0.16]), therefore the numerical difference between these effects may not be statistically significant. However, when comparing directly the sites of maximal amplitude for this response (Fz), the deficit was seen in cMMN amplitudes from the dual rule paradigm, but not in duration MMN amplitudes from the optimal paradigm. Therefore, at the site of maximal amplitude for this response, a cMMN reduction elicited by the dual rule paradigm is significant, while a duration MMN deficit elicited by the optimal paradigm is not significant.

Finally, our hypothesis that MMN amplitudes from the optimal multi-feature paradigm would be related to more severe psychosis symptoms in the EPP group was not supported. Significant correlations in the opposite direction were found between both positive and negative psychosis symptoms. Similarly, our hypothesis that more severe psychosis symptoms and measures of functioning would be related to reduced cMMN amplitudes was also not confirmed.

More severe auditory hallucinations were related to greater cMMN amplitudes, and there were no relationships between functioning scale scores and cMMN amplitudes.

Chapter 4: Discussion

The current study was the first account of the cMMN response to a novel dual rule cMMN paradigm in individuals with EPP. This paradigm was hypothesized to have superior sensitivity in detecting auditory processing deficits in EPP due to its increased computational complexity on the cortex. Additionally, the optimal multi-feature MMN paradigm was employed to compare the presence and magnitude of effect between this new paradigm and the classic MMN response that has shown inconsistent deficits in this population.

4.1 Simple MMN Alterations in Early Phase Psychosis

This study added to the varied body of literature on the MMN in response to five different deviant types (duration, frequency, intensity, location, and gap) in this early presentation of the illness. Similar to previous reports (Atkinson et al., 2012; Hermens et al., 2010; Kaur et al., 2012; Oades et al., 2006; Solís-Vivanco et al., 2014; Todd et al., 2008), we found reduced MMN amplitudes in response to duration deviants in our EPP group. Additionally, we did not find significantly reduced MMN amplitudes in the frontal region for any of the other deviant tone types examined (albeit, a significant reduction in MMN amplitude in response to frequency deviants was observed at a central electrode site). This is consistent with the overall impression in the literature that the duration MMN response is the most sensitive to reductions in psychosis that occur early in illness progression, and that other deviant tone types like frequency may only occur with chronicity and therefore are less likely to be seen in EPP (Haigh et al., 2017; Umbricht & Krljes, 2005). It should be noted, however, that the analysis of the optimal MMN paradigm had a small number of EPP participants (n = 13), and a lack of statistical power may have limited our results. A post-hoc power analysis revealed the group comparison for the duration MMN amplitude at Fz achieved a statistical power of $1 - \beta = 0.46$, indicating we had a

54% chance of failing to find a difference between HC and EPP groups if there was one there. This lack of power in our optimal MMN analysis should be considered when interpreting the results.

Interestingly, the MMN response to duration deviants may be more sensitive to alterations in this population because of its computational complexity. The frequency of a tone is processed directly through the cilia on the cochlear membrane and does not require the convergence of information within the cortex (Phillips & Irvine, 1981; Tiitinen et al., 1993). However, processing the duration of a tone uses different, and potentially more complex, neural pathways (Lee et al., 2017). Schizophrenia is a disorder with marked deficits in temporal processing and individuals with schizophrenia may have a longer window of temporal integration for a wide variety of sensory stimuli such as visual stimuli (Haß et al., 2017; Parsons et al., 2013), audio-visual stimuli (Foucher et al., 2007), audio-tactile stimuli (Di Cosmo et al., 2021), and auditory stimuli alone (Carroll et al., 2008; Di Cosmo et al., 2021; Foucher et al., 2007; Todd & Michie, 2000).

It has been hypothesized that the prediction of a missing tone that is required in a missing stimulus cMMN paradigm requires a similar time estimation as the processing of a duration deviant (Salisbury & McCathern, 2016). Moreover, the integration of acoustic information over time results in a perceived loudness increment in the tone (Scharf, 1978). Therefore, the processing of a duration deviant may also include the perceived increase in the intensity of the tone, making it similar to a double deviant (duration and intensity) cMMN paradigm. This more complex computational demand on the cortex to process duration deviants would explain why the duration MMN response has the highest effect size of any MMN response (Umbricht & Krljes, 2005). However, it must be noted that while the duration MMN has the highest effect size

out of all of the MMN responses, there are still inconsistencies across studies that examine this response. Even in studies that were conducted in the same clinic and with the same equipment as the current study, conflicting reports of no duration MMN reductions exist (Fisher et al., 2018). Furthermore, the effect sizes viewed with the dual rule complex MMN paradigm (*Hedges' g* = 0.95) are superior to those reported with the duration MMN (*Hedges' g* = 0.82), further supporting the hypothesis that a cMMN reduction elicited by the dual rule paradigm is much greater in this population, and therefore reports of reductions may be more robust and resistant to the inconsistencies seen with the duration MMN. Ultimately, moving toward complex MMN paradigms are likely the key to allowing us to view larger deficits of auditory processing in psychosis that may provide us with the sensitivity required to utilize this response as a biomarker.

When considering the clinical implications of an MMN reduction in psychosis, it would make sense that a reduction in this response could be related to psychotic symptoms such as withdrawal and isolation. The generation of an MMN is one of the first steps in the auditory sensory processing stream (Näätänen et al., 2004). Therefore, a reduction in the strength or generation of an MMN response would affect an individual's ability to produce the subsequent brain responses in that sensory processing stream, like the P3a and P3b responses that ensure appropriate attentional allocation to relevant stimuli (Polich, 2007). On a behavioral level, an MMN deficit could be related to a lack of attention drawn to external events, or reduced response times on behavioral tasks (Javitt et al., 1995).

Auditory deviants occur in our surrounding environment constantly. When functioning properly, the MMN system can aid in the processing of those environmental changes and foster a drive to explore one's environment (Javitt et al., 1995). When not functioning properly, this

could contribute to less of that natural drive to explore, and could result in withdrawal from novel experiences, which aligns with the negative psychosis symptomology of social withdrawal and social anhedonia. However, we found significant correlations between SOFAS scores and MMN amplitudes in response to all deviant tone types except for intensity, where higher social and occupational functioning was related to a greater reduction of the MMN response. This is counter-intuitive to what we would expect to see.

It is possible our EPP sample did not represent a patient cohort with high levels of social withdrawal (the average SOFAS scores for the EPP group in this analysis were 66.2, indicating only some functional difficulties), and our lack of variance in social functioning is driving these correlations. This serves to reinforce the fact that the MMN response in this population is quite heterogeneous, and adds to the varied literature on this response.

4.2 Relationship Between the MMN Response, Psychosis Symptoms, and Functioning

A reduction in MMN amplitudes in our EPP group was related to less severe psychosis symptoms. This finding does not support our original hypothesis that an MMN deficit is more representative of a state marker of more severe illness, rather than a trait marker indicative of illness vulnerability. When NMDA receptor blockers are administered, the frequency MMN reduction seen in chronic schizophrenia improves (Lavoie et al., 2008). This suggests that the frequency MMN response functions like a trait marker of psychotic illness, and this hypothesis has been supported in previous literature (Devrim-Üçok et al., 2008). However, our findings suggest the opposite effect, and that worse psychotic illness improves the MMN response.

There are a few possible explanations for this finding. First, perhaps our EPP sample (92% of which were receiving antipsychotic medication) did not capture a wide enough breadth of psychosis symptom severity to detect this previously reported brain-behaviour connection. Our

minimum and maximum reported PSYRATS total scores were 0 and 32 (out of a possible 44). Further, our average SOPS scores did not exceed 2.5 for any individual subscale, suggesting that on average, our group was mild-to-moderately symptomatic on each scale. If a relationship between increased psychotic symptoms and an MMN reduction is only present at levels of moderately severe illness or above, then our sample would not have allowed us to capture that effect. Second, the utilization of the SOPS as our measure of psychosis symptom severity may have influenced this result. Although SOPS scores are highly correlated with PANSS scores in an EPP sample (Tso et al., 2017), the previous study that reported the correlation opposite to the one found here did not use the SOPS measure to determine symptom severity, but rather used the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS; Oades et al., 2006). Therefore, the correlational findings may differ depending on the scale of symptom severity used, and the current study's utilization of the SOPS may have influenced the counterintuitive correlations. Third, the sample size of our optimal MMN analysis was small, and it is possible that the previously mentioned lack of power seen in this analysis limited our ability to examine these relationships. Finally, it is possible that the MMN response is still indicative of a trait marker of psychotic illness, and that our finding was spurious. Undeniably this correlational finding is curious and demands further investigation to see if there are indeed contributing factors we did not capture here.

4.3 Reduced Complex MMN Amplitudes in EPP

Our hypothesis that cMMN amplitudes elicited by the dual rule paradigm would be reduced in EPP compared to healthy controls was supported. We found an overall reduction of cMMN amplitudes in the frontal region over the cortex, as well as a statistically significant reduction in amplitude with a large effect size (*Hedges' g* = 0.95) at the site of maximal amplitude for this

ERP (Fz). Although this was the first study to employ the dual rule cMMN paradigm, these reported reductions are similar to previous studies that have found reduced cMMN amplitudes in EPP using different paradigms to elicit the cMMN response (Hay et al., 2015; Perez et al., 2014; Rudolph et al., 2015; Salisbury et al., 2020). However, the effect size viewed in the current study does appear to be superior to that reported in the recent meta-analysis by Avissar and colleagues (2018) on the previously reported cMMN deficits in schizophrenia (*Hedges' g* = 0.59; Avissar et al., 2018). Although the meta-analysis provides a higher level of evidence than the current cohort study, this could indicate the dual rule cMMN paradigm is indeed providing a more sensitive measure of the cMMN response. Additionally, unlike the optimal MMN paradigm analysis, the post-hoc power analysis for the dual rule paradigm revealed the differences detected between HC and EPP groups in cMMN amplitudes at Fz achieved adequate statistical power ($1 - \beta = 0.80$). More studies exploring this paradigm across the illness phase are required to confirm this hypothesis.

A reduced cMMN response in individuals within the early phase of psychosis may shed light on the underlying neural correlates of the clinical presentation of the illness. To generate a cMMN response effectively, one must be able to utilize patterns to make sense of the external environment and make predictions about what the next incoming stimulus will be. This complex pattern analysis must occur quickly, and preattentive/non-purposefully. To hold a successful social interaction, the same mechanisms must be employed to ensure the prediction of what will come next by using context cues in the dialogue. The current finding that this ability is altered in psychosis would support the clinical presentation of the lack of social functioning we commonly see in the illness (Salisbury & McCathern, 2016). Previous reports of the cMMN in response to a missing stimulus paradigm showed higher cMMN amplitudes were related to better utilization of

social skill sets (Salisbury et al., 2020), and those with chronic schizophrenia who showed lower cMMN amplitudes had a lack of spontaneity of speech and flow in conversation (Haigh et al., 2016). However, we did not find any significant correlations between the cMMN response and social functioning in the EPP group. It is possible that our sample did not capture a wide breadth of social functioning deficits (our average SOFAS score for this analysis was 67.5 [±22.0], indicating only some difficulty in social functioning, but generally functioning well). Future studies with more severely ill patient samples may help clarify this phenomenon.

The underlying neural correlates of this deficit in the cMMN response likely lie within the well-established neurological abnormalities of schizophrenia. Specifically, widespread cortical grey matter loss and reduced cortical thickness (including in the temporal region, which is necessary for MMN generation) have been seen in both chronic schizophrenia (Aoyama et al., 2011; Stan et al., 2020; Velakoulis et al., 2002) as well as early presentations of the illness (Gallardo-Ruiz et al., 2019; Théberge et al., 2007; Whitford et al., 2005). Decreased dendritic spine density in the dorsolateral prefrontal cortex (dlPFC) is also reported in chronic schizophrenia (Glantz & Lewis, 2000). Due to the loss of synaptic density in these regions, individuals experiencing psychosis may lack the cortical infrastructure necessary to complete the complex pattern predictions required to generate a cMMN response. Moreover, Rasser et al. (2011) found that reduced grey matter in the temporal and frontal cerebral regions was related to reduced MMN amplitude in response to frequency and duration deviants in patients with chronic schizophrenia (Rasser et al., 2011), further supporting the idea that these illness-related changes in cortical grey matter are underlying the inability to produce a strong cMMN response.

Additionally, widespread dysfunction of the glutamatergic system may also underlie these cMMN deficits. Although there have been no studies examining the effects of NMDA blockers

on the cMMN response, the current assumption is that similar to the MMN response, the cMMN response relies on the healthy functioning of these receptors and the glutamatergic system. Alterations in glutamate levels have been reported in EPP (reviewed in Bissonnette et al., 2022). Therefore, this alteration of glutamatergic activity in the auditory cortex is potentially related to this inability to generate a strong cMMN response. Future studies examining the link between glutamate and the cMMN response are needed to confirm this assumption.

Nonetheless, if it is true that glutamatergic dysfunction is underlying this deficit, there is reason to believe that this alteration may also be present in a high-risk sample. Mössner and colleagues (2009) followed a CHR sample in a longitudinal design and found those with an alteration to the DAOA/G72 gene (a gene associated with NMDA receptor function) were more likely to convert to psychosis. A recent meta-analysis examining cerebral glutamate levels in CHR and GHR individuals found lower glutamate in the thalamus of a CHR sample, and higher Glx in the frontal region of GHR individuals (Wenneberg et al., 2020). Further, Stone and colleagues (2009) reported reduced glutamate in the thalamus of CHR individuals was associated with less grey matter in the temporal region, a key region involved in MMN generation. This evidence highlights the importance of examining the cMMN response in a high-risk population moving forward.

4.4 Relationship Between the cMMN Response, Psychosis Symptoms, and Functioning

Our hypothesis that cMMN amplitudes would be related to social and occupational functioning was not supported. Instead, we found no correlations between SOFAS or GAF scores and the cMMN response. One reason why we may have failed to find significant correlations between functioning scale scores and the cMMN response is because we did not capture a wide enough variety of patient functioning in our sample. Our EPP sample was

comprised of all community-dwelling out-patient individuals. It is possible that correlations with functioning and the cMMN response become apparent at lower levels of functioning, and including individuals who are hospitalized or in-patient would have allowed us to capture a wider breadth of functioning to reveal that brain-behaviour association.

Our hypothesis that cMMN amplitudes would be related to psychosis symptoms was partially supported. When examining correlations with psychosis symptom scales, we found higher cMMN amplitudes were related to increased severity of positive, but not negative psychosis symptoms. Specifically, higher reported auditory hallucinations (measured by the PSYRATS and SOPS) were related to increased cMMN amplitudes. This finding is opposite to what we would expect to see if a reduced cMMN response was representative of illness progression.

Although this correlational finding seems counterintuitive, more severe positive psychosis symptoms being related to a less severe deficit in auditory processing is not unheard of. Fisher et al. (2012) reported an association between increased MMN amplitudes in response to gap deviants and an increased loudness, duration, and clarity of auditory hallucinations (Fisher et al., 2012). They hypothesized that this relationship could be due to hyperexcitability of the areas of generation for the MMN during the passive listening task. There is evidence to suggest varying environmental conditions during the passive listening task can alter the MMN response (Muller-Gass et al., 2005). Although all participants were subjected to the same surrounding environment during the task, participants actively experiencing auditory hallucinations may have experienced increased activation in the regions responsible for cMMN generation, thus resulting in increased neural activity contributing to this association.

Additionally, considering the high amounts of previous traumatic events reported by our EPP group, is it possible that the effects of that trauma have caused considerable and prolonged stress

on the nervous system in these individuals (Sherin & Nemeroff, 2011). Chronic stress can condition the nervous systems to be prone to hyperexcitability (Sharp, 2017), which may have contributed to the increased cMMN response we observed in our EPP group (Menning et al., 2008). Alternatively, it is also possible that auditory hallucinations (or something about their underlying cortical effects) are mediating the reduction of cMMN response that occurs in the illness, and are serving as protective factors against this reduction.

Despite various possible interpretations of these findings, the underlying cause of this association is speculative and still largely unclear. However, although this association is present between more auditory hallucinations and an increased cMMN response, group comparisons still showed reduced cMMN amplitudes in patients compared to controls overall. This ultimately suggests that whatever is driving this association between increased cMMN and psychosis symptomology is not strong enough to surpass deficits caused by the illness.

4.5 Moving Forward with the cMMN

This study was the first step in determining the clinical utility of the cMMN response elicited by the dual rule paradigm as a biomarker for the early detection of psychosis. This exploration is incredibly valuable considering the importance of early detection and intervention for patient outcomes, and the potentially damaging effects of those interventions if employed in individuals who would not go on to develop psychosis if left untreated (McGlashan et al., 2006; McGorry et al., 2002). Moreover, simply being labeled “at-risk” for a psychotic syndrome can be damaging due to the very real stigma that exists in our society (Yang et al., 2010). Having a biomarker with appropriate sensitivity that can be easily utilized in a clinical setting would certainly help to alleviate some of that damage.

Despite considerable scientific efforts to pin down an ERP that can be used as a biomarker for psychosis risk, there has been little to no implementation of these tools in practice (Campanella, 2021; Studerus et al., 2017). Two main reasons for this stagnation have been suggested by Campanella (2021). First, the heterogeneity of data across studies raises questions about the reliability of these measures. To address this concern, the movement toward a standardized ERP battery (such as ERP CORE, a free online resource) that can be used across labs and clinics, and that would allow for direct comparison of data across sites is warranted (Kappenman et al., 2021). To date, these guides typically include instructions on giving the optimal multi-feature MMN paradigm (identical to what has been presented in the current study) but do not include specific guidelines for eliciting a cMMN (Duncan et al., 2009). The dual rule cMMN paradigm that has been employed here shows may be included in these standardized batteries following further exploration in chronic and high-risk samples.

The second factor affecting the lack of implementation of ERPs as psychosis biomarkers in clinical settings is the low specificity of these ERP alterations. For example, reductions in the MMN response have also been robustly reported in bipolar disorder with psychotic features (Raggi et al., 2022). This overlap likely has something to do with our current DSM-5 diagnostic classification system that attempts to view different mental illnesses as discontinuous entities each with their own set of symptoms, when in fact there is considerable overlap and co-morbidity of symptomology and neurological etiology across disorders (Krueger & Eaton, 2015). Nonetheless, ERPs such as the MMN still hold value when assessing risk. To address this issue of low specificity, considering the multivariate endophenotype model has been suggested (Price et al., 2006).

The multivariate endophenotype model suggests that using a combination of multiple ERPs (or neuroimaging techniques) can provide better predictive validity of conversion than simply one marker on its own. Additional ERPs that have shown marked deficits in psychosis and could be used alongside the cMMN as psychosis predictors include the P50 sensory gating response (Sánchez-Morla et al., 2008), and the P300 response (Kaur et al., 2012; Nagai et al., 2013). Other neuroimaging techniques like magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (H-MRS) could also be used in these predictive models. Cortical grey matter loss in the temporal region has shown some predictive capability in GHR samples (Job et al., 2006), and glutamate reductions in the anterior cingulate cortex measured with H-MRS have also been suggested to have some predictive capability in CHR samples (Egerton et al., 2014).

4.6 The Effects of Trauma and Substance Use on the MMN and cMMN Response

The number of adverse events reported on the TALE was significantly higher in our EPP group compared to the HC group. This adds to the growing body of research on the prevalence of trauma in psychosis and supports the notion that research on this population should consider the potential confounding effects of past trauma on results (Schäfer & Fisher, 2022). Although there have been reports of increased MMN amplitudes in individuals with post-traumatic stress disorder (Bangel et al., 2017; Ge et al., 2011), these results are largely inconsistent and reduced MMN amplitudes (Menning et al., 2008) and no alterations to MMN amplitudes have also been reported (Löw et al., 2019). Additionally, to our knowledge, there have been no studies examining the MMN response in individuals with psychosis and co-morbid post-traumatic stress disorder. Therefore, our exploration of the relationship between the prevalence of trauma in our EPP group and the cMMN and MMN response was exploratory. Accordingly, we found no

significant correlations between the cMMN or MMN responses and TALE scores in either the HC or EPP groups.

This seems to suggest that the role of trauma in psychosis is relatively independent of the neurological underpinnings that are contributing to auditory change detection deficits. However, again, it is possible that the relative low symptom severity of our EPP sample could have influenced these results. Moving forward, more research with a greater depth of measure for trauma and its subsequent effects on the individual would be beneficial. Our measure of trauma was only focused on the prevalence of events throughout the lifetime, and did not include the consideration of variables that could mediate the negative effects of trauma, like emotional support, and subjectively perceived distress from the events. Mixed-methods studies incorporating qualitative data alongside these neurophysiological measures may be of interest to researchers moving forward to examine this further.

When examining the relationship between average reported weekly substance use and the recorded neurophysiological variables, we did not find any correlations between the frequency of cannabis use and neither the cMMN nor MMN response. We did, however, find a relationship between higher reported weekly alcohol consumption and reduced MMN amplitudes in response to the frequency deviant. This is consistent with previous reports of increased chronic alcohol intake and an attenuated frequency MMN amplitude in EPP and may be representative of alcohol's additive effect on NMDA receptor hypofunction (Chitty et al., 2011; Ramlakhan et al., 2018). To our knowledge, this is the first study to examine the relationship between the cMMN response and alcohol use, and the same relationship was found where higher reported weekly alcohol use was related to lower cMMN amplitudes. This would make sense considering the

conceptualization of the cMMN response as being dependent on NMDA receptors as well, and the animating effects of alcohol on those receptors (Chandrasekar, 2013).

4.7 Limitations

This study is not without its limitations. First, the sample size was modest. Although we were able to detect significant differences with large effect sizes with the current sample, these findings must be replicated with larger samples. Particularly with the optimal MMN analysis, where a post-hoc power analysis revealed insufficient power to detect differences in this measure given our current sample size. Second, our measure of psychosis symptoms in the EPP group (the SOPS) was validated in a prodromal population and was modified from the PANSS to include a wider breadth of symptoms. The decision to utilize this measure in our EPP group was to allow for direct comparison with a high-risk group, which will be collected in the future. Therefore, our correlational analysis with this symptom scale should be interpreted with caution. Finally, we relied on self-report retrospective measures of cannabis and alcohol use which were likely sensitive to bias. A more in-depth measure of substance use (such as the timeline follow-back method) would have provided a better measure of substance use in this population.

4.8 Future Directions

Apart from validating the dual-rule paradigm in larger samples of individuals with EPP and those with chronic schizophrenia, future studies should employ the dual rule cMMN paradigm in a sample of at-risk individuals (both clinically and genetically). First, to determine if there are deficits in these populations, and then to include follow-up time points to complete the stratification of individuals into converters and non-converters. This would allow for an odds ratio analysis to be completed to determine if the predictive capability of the cMMN response elicited by this paradigm is superior to traditional prediction methods of prodromal symptoms

alone. Additionally, by including multiple follow-up time points, we could see if the cMMN response elicited by this paradigm is affected by factors like antipsychotic treatment, psychosis symptom amelioration or deterioration, and illness duration. This could lead to future inquiries on the potential of a cMMN alteration as a marker of treatment efficacy in this population.

To better understand the cMMN response, and how it deviates computationally from the MMN response, future studies should consider using fMRI measures alongside the dual rule cMMN paradigm to determine the exact location of generation for this response. Further, using H-MRS data to examine the link between this response and glutamate levels in the cortex (specifically in the temporal and frontal regions) would allow us to confirm that this response is indeed dependent on NMDA receptor function similar to the MMN response. Alternatively, this could also be explored in a study design where the cMMN response is measured following the administration of NMDA receptor antagonists (i.e. ketamine).

4.9 Conclusion

This study provided the first account of cMMN amplitudes in response to a novel dual rule cMMN paradigm that breaks two abstract pattern rules simultaneously. We found significantly reduced cMMN amplitudes in an early phase psychosis sample using this paradigm, and the observed effect size of this reduction provides promising evidence that this paradigm may be a more sensitive marker to reliably detect auditory processing deficits in this population that may be used as biomarkers for psychosis vulnerability in future predictive models. We also explored the MMN response to five deviant tone types in this sample, and our results corroborated previous findings of reduced duration MMN, but no significant reductions for any other deviant tone type in the frontal region. This supports the growing idea that MMN

alterations are not reliable markers of psychosis risk, and are not robustly present in early presentations of the illness.

Our correlational analyses showed that increased positive and negative psychosis symptoms were related to increased MMN and cMMN amplitudes. This finding is counterintuitive to the effect we hypothesized we would see, and seemly goes against the neurological underpinnings of this deficit that include alternations to grey matter volumes and glutamate levels in this population. However, potential explanations for these findings include the illness severity of our sample and the possibility that we captured hyperexcitability of the cortex in this sample.

Furthermore, this study provides descriptive information on the prevalence of trauma in psychosis, thus adding to the growing body of literature on the role of trauma in psychosis. This study was also to the best of our knowledge the first to examine the link between the amount of self-reported previous traumatic experiences and the cMMN and MMN responses. We found that the prevalence of past traumatic experiences appears to be independent of these pre-attentive sensory processing measures. Moving forward, the cMMN response elicited by the dual rule paradigm should be further examined in high-risk populations to explore its predictive capability and to access its potential role in a multivariate endophenotypic model of prediction for psychosis vulnerability.

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Table 1.

Group Comparison of Demographic Variables Used in the MMN Analysis.

	EPP (*n* = 13)	**HC (*n* = 17)**	***t*(df)**	***p*-value**
Age (years)	22.7 (±2.3)	23.1 (±2.4)	t(28) = 0.498	.622
Sex (M/F)	8/5	5/12		
Level of education (years)	13.0 (±2.9)	14.8 (±2.0)	t(28) = 1.949	.061
Weekly alcohol consumption (drinks per week)	3.6 (±5.6)	3.2 (±2.9)	t(28) = -0.228	.821
Weekly cannabis consumption (times consumed per week)	3.0 (±3.1)	1.0 (±2.2)	t(28) = -1.982	.057
TALES	9.7 (±3.5)	4.9 (±3.4)	t(28) = -3.735	< .001**
SOFAS	66.2 (±22.3)	90.7 (±6.9)	t(28) = 4.297	< .001**

Note. This table displays the mean (± standard deviation) values for demographic variables collected in both the healthy control (HC) and early phase psychosis (EPP) groups for the MMN analysis. The Trauma and Life Events Checklist (TALES) and Social and Occupational Functioning Assessment Scale (SOFAS) are also shown.
** Indicates a statistically significant difference between groups on an independent samples t-test at the $p < .05$ level.

Table 2.

Early Phase Psychosis Clinical Variables Used in the MMN Analysis.

	M (±SD)
Medication Status (medicated/non-medicated)	(12/1)
GAFS	66.2 (±22.3)
PSYRATS	
Total	13.3 (±12.7)
Distress	6.6 (±7.0)
Frequency	2.8 (±2.9)
Attribution	2.5 (±2.3)
Loudness	1.6 (±1.6)
SOPS	
Unusual thought content/delusional ideas (P1)	2.2 (±1.9)
Suspiciousness/persecutory ideas (P2)	2.1 (±1.6)
Grandiose ideas (P3)	0.7 (±1.4)
Perceptual abnormalities/hallucinations (P4)	2.2 (±1.8)
Disorganized communication (P5)	1.6 (±1.8)
Social Anhedonia (N1)	1.9 (±2.0)
Avolition (N2)	1.6 (±1.6)
Expression of emotion (N3)	1.1 (±1.3)
Experience of emotions and self (N4)	1.4 (±1.7)
Ideational richness (N5)	0.9 (±0.9)
Occupational functioning (N6)	2.3 (±2.4)

Note. Average (±standard deviation) scores on the Global Assessment of Functioning Scale (GAFS), Psychotic Symptoms Rating Scale (PSYRATS), and Scale of Prodromal Symptoms (SOPS) in the early phase psychosis sample used in the MMN analysis (n = 13).

Table 3.

Group Comparison of Mean Amplitudes and Latencies from the Duration Deviant

				Duration		
		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-2.31	1, 28	13.778	4.859	.036*
	EPP	-0.95				
Fz	HC	-2.55	1, 28	9.222	2.458	.128
	EPP	-1.43				
F4	HC	-2.51	1, 28	8.210	2.758	.108
	EPP	-1.45				
C3	HC	-2.16	1, 28	6.662	2.286	.142
	EPP	-1.21				
Cz	HC	-3.19	1, 28	19.063	2.676	.113
	EPP	-1.58				
C4	HC	-2.51	1, 28	7.967	2.330	.138
	EPP	-1.47				
		Mean (ms)	***df***	**95% *CI* (lower bound, upper bound)**	***t***	***p*-value**
Latency (Fz)	HC	184.65	26	(-0.347, 1.155)	1.075	.204
	EPP	180.85				

Note. All values for MMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

Table 4.

Group Comparison of Mean Amplitudes and Latencies from the Frequency Deviant

				Frequency		
		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-1.97	1, 28	1.725	0.568	.458
	EPP	-1.48				
Fz	HC	-2.3	1, 28	6.183	2.003	.168
	EPP	-1.43				
F4	HC	-2.43	1, 28	10.215	3.503	.072
	EPP	-1.25				
C3	HC	-1.95	1, 28	6.127	3.511	.071
	EPP	-1.04				
Cz	HC	-2.49	1, 28	15.637	2.747	.109
	EPP	-1.03				
C4	HC	-2.37	1, 28	16.733	4.195	.050*
	EPP	-0.86				
		Mean (ms)	***df***	**95% *CI* (lower bound, upper bound)**	***t***	***p*-value**
Latency (Fz)	HC	167.53	26	(-0.708, 0.778)	0.093	.181
	EPP	173.46				

Note. All values for MMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

Table 5.

Group Comparison of Mean Amplitudes and Latencies from the Intensity Deviant

				Intensity		
		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-1.48	1, 28	0.787	0.287	.596
	EPP	-1.16				
Fz	HC	-1.95	1, 28	0.774	0.290	.594
	EPP	-1.63				
F4	HC	-1.91	1, 28	1.307	0.534	.471
	EPP	-1.49				
C3	HC	-1.74	1, 28	5.658	1.531	.226
	EPP	-0.86				
Cz	HC	-2.25	1, 28	7.688	2.011	.167
	EPP	-1.23				
C4	HC	-2.14	1, 28	4.881	1.819	.188
	EPP	-1.33				
		Mean (ms)	***df***	**95% *CI* (lower bound, upper bound)**	***t***	***p*-value**
Latency (Fz)	HC	186.47	26	(-0.688, 0.797)	0.145	.883
	EPP	182.38				

Note. All values for MMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

Table 6.

Group Comparison of Mean Amplitudes and Latencies from the Gap Deviant

				Gap		
		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-2.08	1, 28	0.111	0.044	.835
	EPP	-1.96				
Fz	HC	-2.40	1, 28	1.380	0.516	.478
	EPP	-1.97				
F4	HC	-2.50	1, 28	4.231	1.805	.190
	EPP	-1.74				
C3	HC	-1.82	1, 28	2.141	0.930	.930
	EPP	-1.29				
Cz	HC	-2.66	1, 28	11.159	1.725	.200
	EPP	-1.43				
C4	HC	-2.17	1, 28	7.876	2.162	.153
	EPP	-1.14				
		Mean (ms)	***df***	**95% *CI* (lower bound, upper bound)**	***t***	***p*-value**
Latency (Fz)	HC	185.71	26	(-1.070, 0.426)	-0.857	.337
	EPP	200.00				

Note. All values for MMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

Table 7.

Group Comparison of Mean Amplitudes and Latencies from the Location Deviant

				Location		
		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-1.35	1, 28	6.191	3.674	.066
	EPP	-0.43				
Fz	HC	-1.45	1, 28	0.640	0.281	.601
	EPP	-1.16				
F4	HC	-1.21	1, 28	0.036	0.017	.899
	EPP	-1.14				
C3	HC	-1.47	1, 28	1.777	0.781	.384
	EPP	-0.98				
Cz	HC	-1.92	1, 28	5.544	1.095	.304
	EPP	-1.06				
C4	HC	-1.57	1, 28	2.043	0.672	.419
	EPP	-1.05				
		Mean (ms)	***df***	**95% *CI* (lower bound, upper bound)**	***t***	***p*-value**
Latency (Fz)	HC	157.65	26	(-1.290, 0.223)	-1.421	.267
	EPP	176.46				

Note. All values for MMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

Table 8.

Group Comparison of Demographic Variables Used in the cMMN Analysis.

	EPP (*n* = 14)	**HC (*n* = 15)**	***t*(df)**	***p*-value**
Age (years)	22.9 (±2.2)	23.1 (±2.5)	t(27) = 0.236	.816
Sex (M/F)	9/5	4/11		
Level of education (years)	12.9 (±2.8)	14.6 (±2.1)	t(27) = 1.811	.081
Weekly alcohol consumption (drinks per week)	3.3 (±5.5)	3.5 (±3.0)	t(27) = 0.078	.938
Weekly cannabis consumption (times consumed per week)	2.8 (±3.1)	1.2 (±2.3)	t(27) = -1.554	.132
TALES	9.3 (±3.7)	4.5 (±3.0)	t(27) = -3.771	< .001**
SOFAS	67.5 (±22.0)	90.1 (±4.7)	t(27) = 4.226	< .001**

Note. This table displays the mean (± standard deviation) values for demographic variables collected in both the healthy control (HC) and early phase psychosis (EPP) groups for the cMMN analysis. The Trauma and Life Events Checklist (TALES) and Social and Occupational Functioning Assessment Scale (SOFAS) are also shown.
** Indicates a statistically significant difference between groups on an independent samples t-test at the $p < .05$ level.

Table 9.

Early Phase Psychosis Clinical Variables Used in the cMMN Analysis.

	M (±SD)
Medication Status (medicated/non-medicated)	(13/1)
GAFS	67.5 (±22.0)
PSYRATS	
Total	13.8 (±12.3)
Distress	7.0 (±6.9)
Frequency	2.9 (±2.8)
Attribution	2.6 (±2.2)
Loudness	1.6 (±1.6)
SOPS	
Unusual thought content/delusional ideas (P1)	2.1 (±1.9)
Suspiciousness/persecutory ideas (P2)	2.1 (±1.5)
Grandiose ideas (P3)	0.6 (±1.3)
Perceptual abnormalities/hallucinations (P4)	2.2 (±1.8)
Disorganized communication (P5)	1.6 (±1.7)
Social Anhedonia (N1)	1.9 (±1.9)
Avolition (N2)	1.6 (±1.6)
Expression of emotion (N3)	1.0 (±1.2)
Experience of emotions and self (N4)	1.4 (±1.6)
Ideational richness (N5)	0.9 (±0.8)
Occupational functioning (N6)	2.1 (±2.4)

Note. Average (±standard deviation) scores on the Global Assessment of Functioning Scale (GAFS), Psychotic Symptoms Rating Scale (PSYRATS), and Scale of Prodromal Symptoms (SOPS) in the early phase psychosis sample used in the cMMN analysis (n = 14).

Table 10.

Group Comparison of Mean Amplitudes and Latencies from the Complex Dual Rule MMN Paradigm.

		Mean (μV)	***df***	**Mean Square**	***F***	***p*-value**
F3	HC	-2.92	1, 27	7.465	1.951	.174
	EPP	-1.90				
Fz	HC	-3.91	1, 27	26.251	6.501	.017*
	EPP	-2.01				
F4	HC	-3.45	1, 27	23.991	4.222	.050*
	EPP	-1.63				
C3	HC	-3.11	1, 27	10.282	0.972	.333
	EPP	-1.92				
Cz	HC	-4.02	1, 27	13.213	0.923	.345
	EPP	-2.67				
C4	HC	-2.87	1, 27	20.681	2.852	.103
	EPP	-1.18				
		Mean (ms)	***df***	**95% *CI***	***t***	***p*-value**
Latency (Fz)	HC	207.73	27	-23.11, 6.29	-1.174	.251
	EPP	216.14				

Note. All values for cMMN amplitude are denoted in microvolts (μV). All values for latencies are denoted in milliseconds (ms).
* $p < .05$

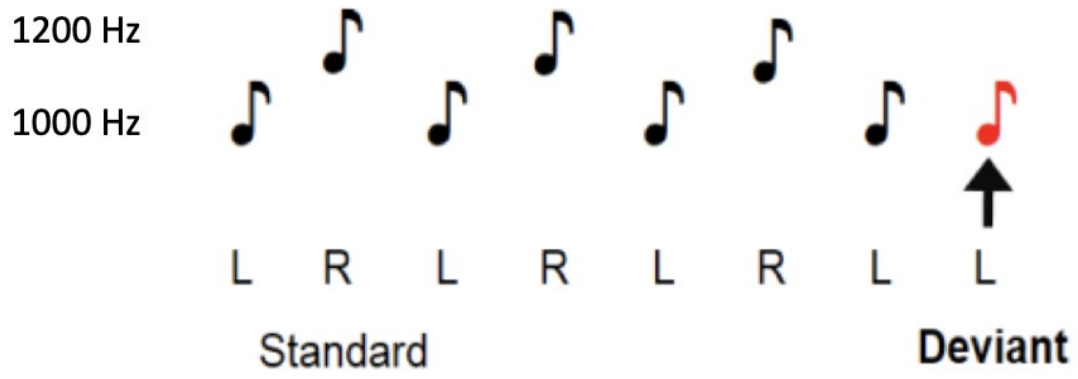
Figure 1.

Visual Representation of the Optimal Multi-Feature Simple MMN Paradigm

Note. The above figure represents the auditory tones presented during the optimal multi-feature MMN paradigm. The black "S" letters represent a presentation of a standard tone, and each red "D" letter represents a presentation of one of the five deviant tone types.

Figure 2.

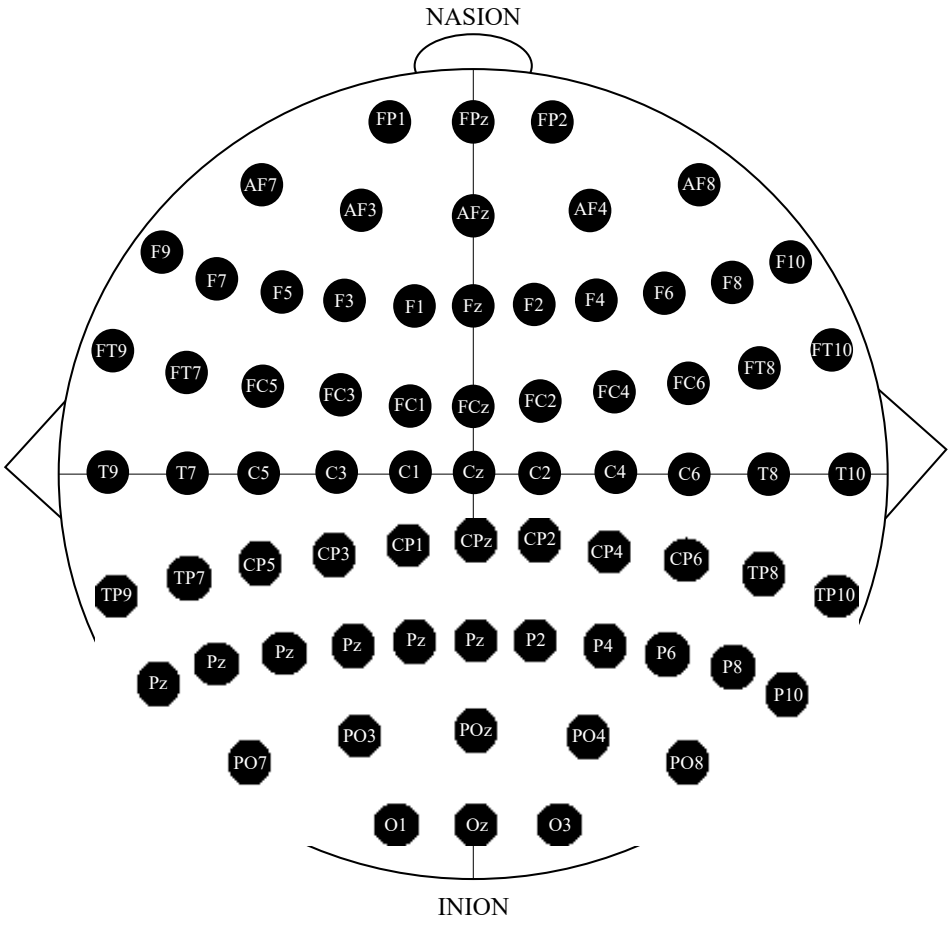
Visual Representation of the Dual Rule Complex MMN Paradigm



Note. The above figure represents the auditory tones played during the dual rule cMMN paradigm. Music notes above a "L" indicate they were played to the left ear, while music notes above a "R" indicate they were played to the right ear. Music notes next to the "1200 Hz" were high-frequency tones while music notes next to the "1000 Hz" low frequency tones. The red music note represents the deviant tone.

Figure 3.

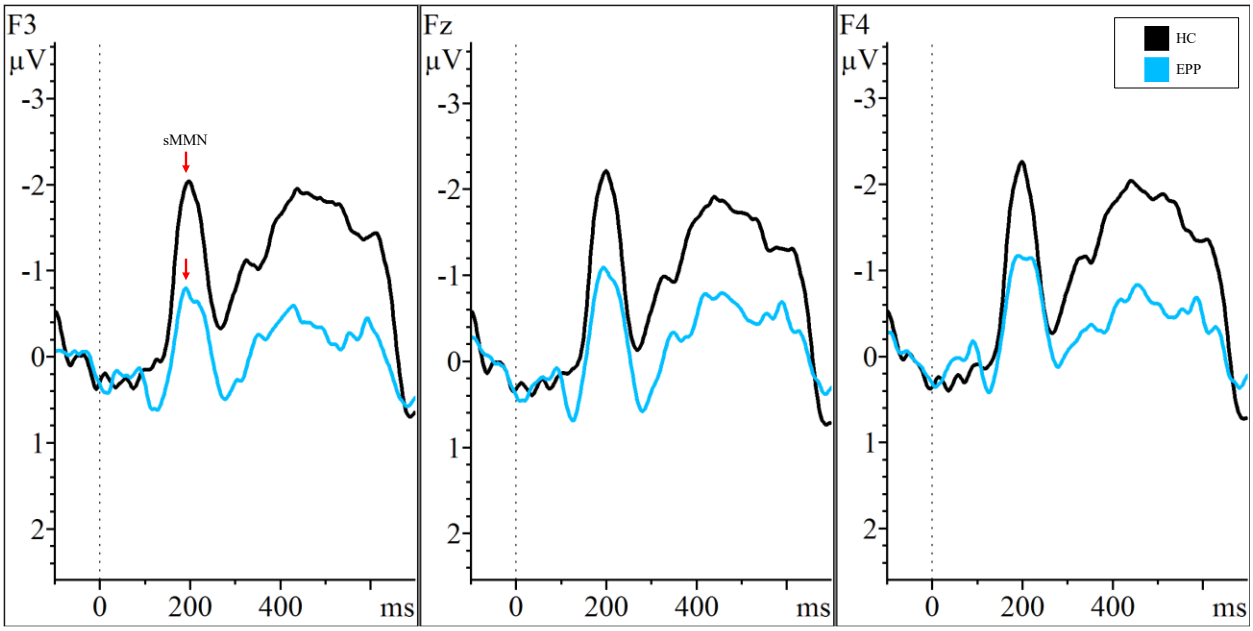
Schematic of the 10-10 System of Electrode Placement



Note. The above figure demonstrates the spatial distribution of electrodes over the scalp according to the 10-10 system of electrode placement.

Figure 4.

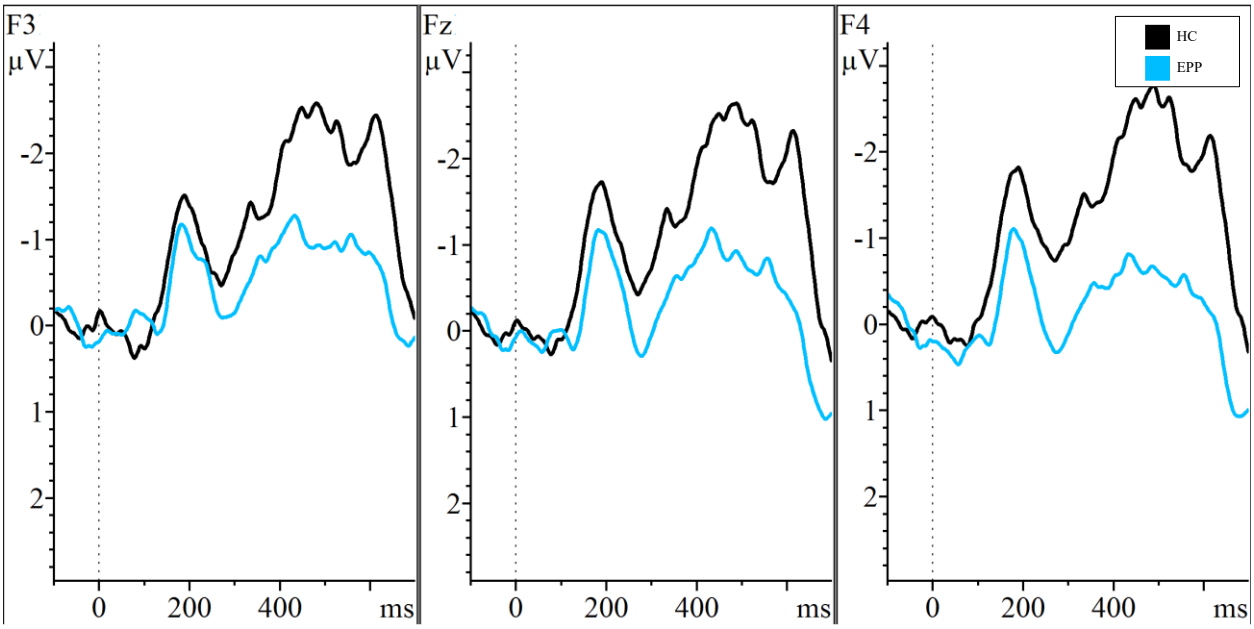
Group Comparison of Duration MMN Response



Note. The above figure demonstrates the average MMN amplitudes in the frontal region in response to duration deviants in the optimal multi-feature MMN paradigm. The black line represents the healthy control group (HC), and the blue line represents the early phase psychosis group (EPP). Statistically significant different amplitudes ($p < .05$) at F3 are marked with the red arrow.

Figure 5.

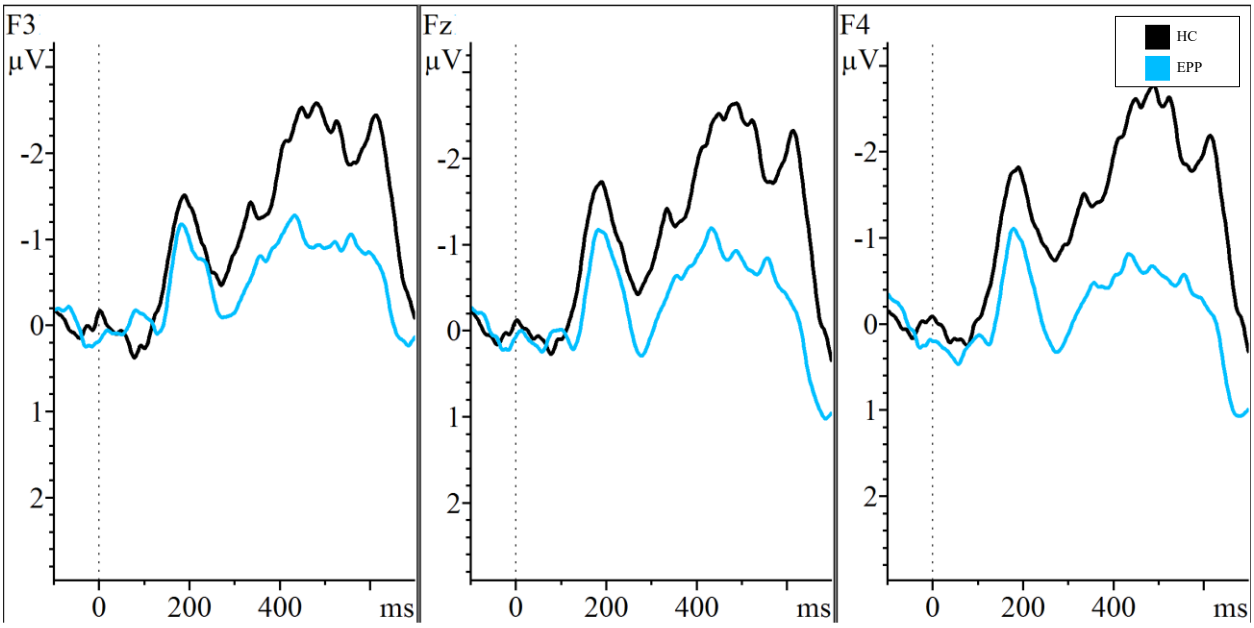
Group Comparison of Frequency MMN Response



Note. The above figure demonstrates the average MMN amplitudes in the frontal region in response to frequency deviants in the optimal multi-feature MMN paradigm. The black line represents the healthy control group (HC), and the blue line represents the early phase psychosis group (EPP). There was no statistically significant difference in amplitude or latency between groups.

Figure 6.

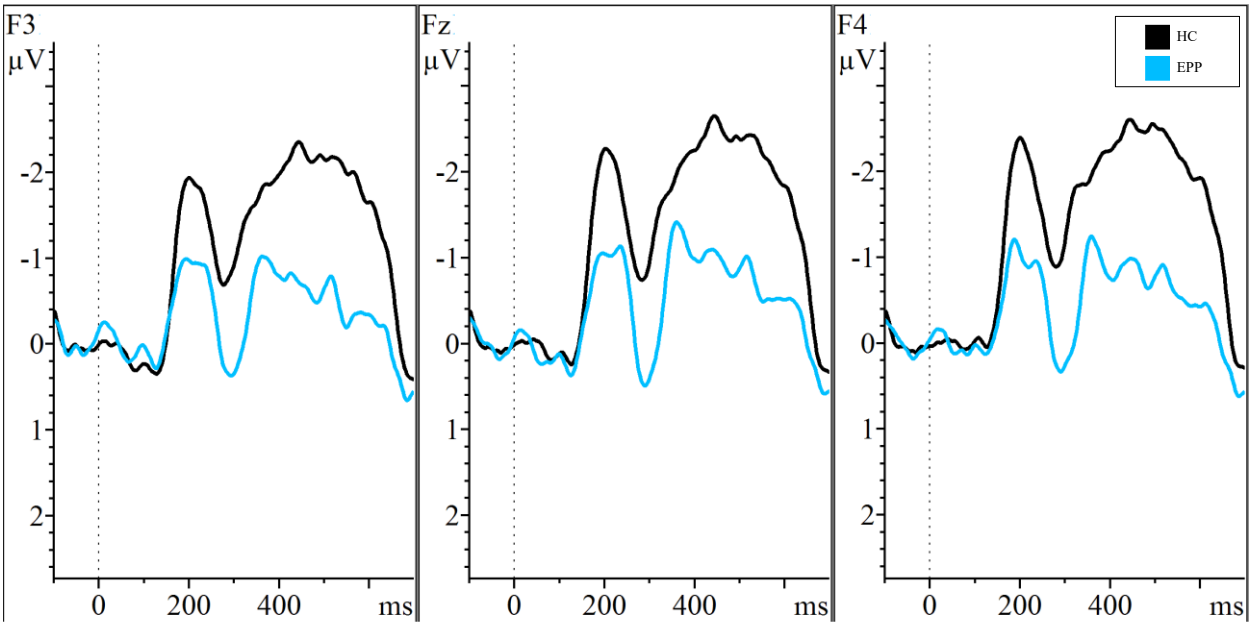
Group Comparison of Intensity MMN Response



Note. The above figure demonstrates the average MMN amplitudes in the frontal region in response to intensity deviants in the optimal multi-feature MMN paradigm. The black line represents the healthy control group (HC), and the blue line represents the early phase psychosis group (EPP). There was no statistically significant difference in amplitude or latency between groups.

Figure 7.

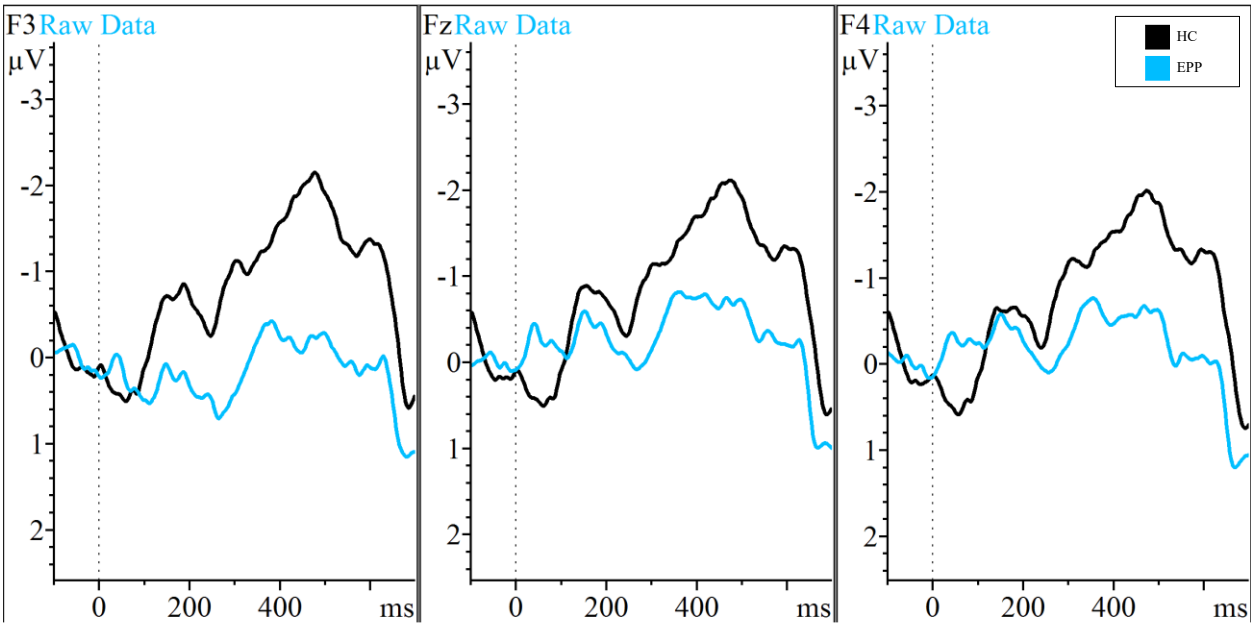
Group Comparison of Gap MMN Response



Note. The above figure demonstrates the average MMN amplitudes in the frontal region in response to gap deviants in the optimal multi-feature MMN paradigm. The black line represents the healthy control group (HC), and the blue line represents the early phase psychosis group (EPP). There was no statistically significant difference in amplitude or latency between groups.

Figure 8.

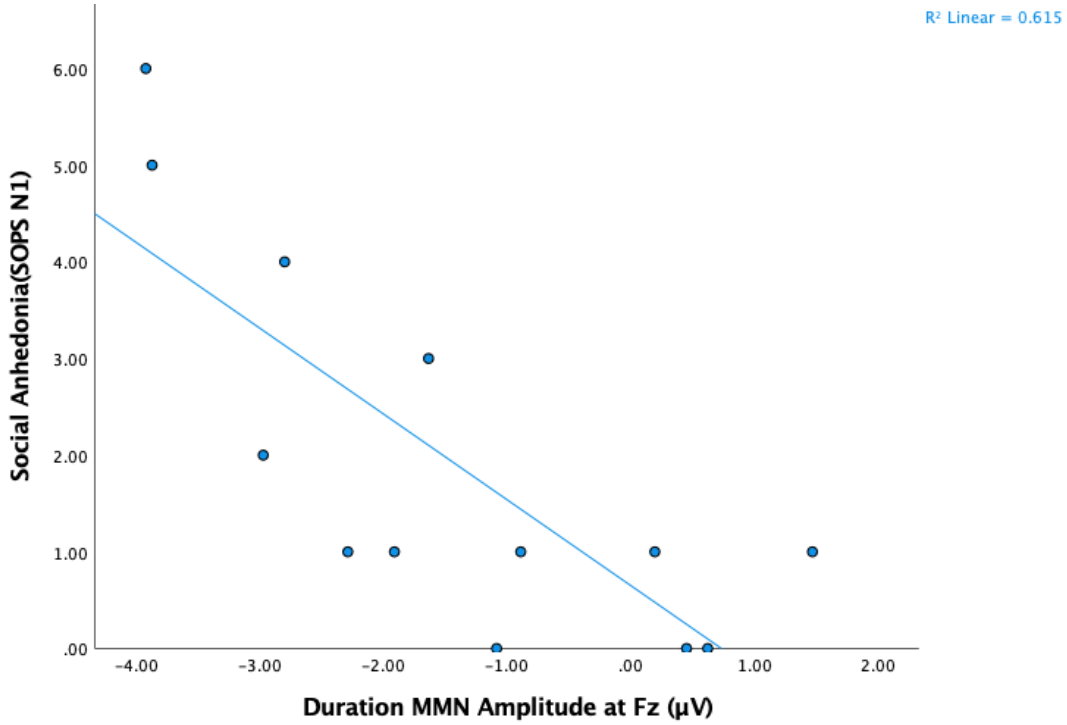
Group Comparison of Location MMN Response



Note. The above figure demonstrates the average MMN amplitudes in the frontal region in response to location deviants in the optimal multi-feature MMN paradigm. The black line represents the healthy control group (HC), and the blue line represents the early phase psychosis group (EPP). There was no statistically significant difference in amplitude or latency between groups.

Figure 9.

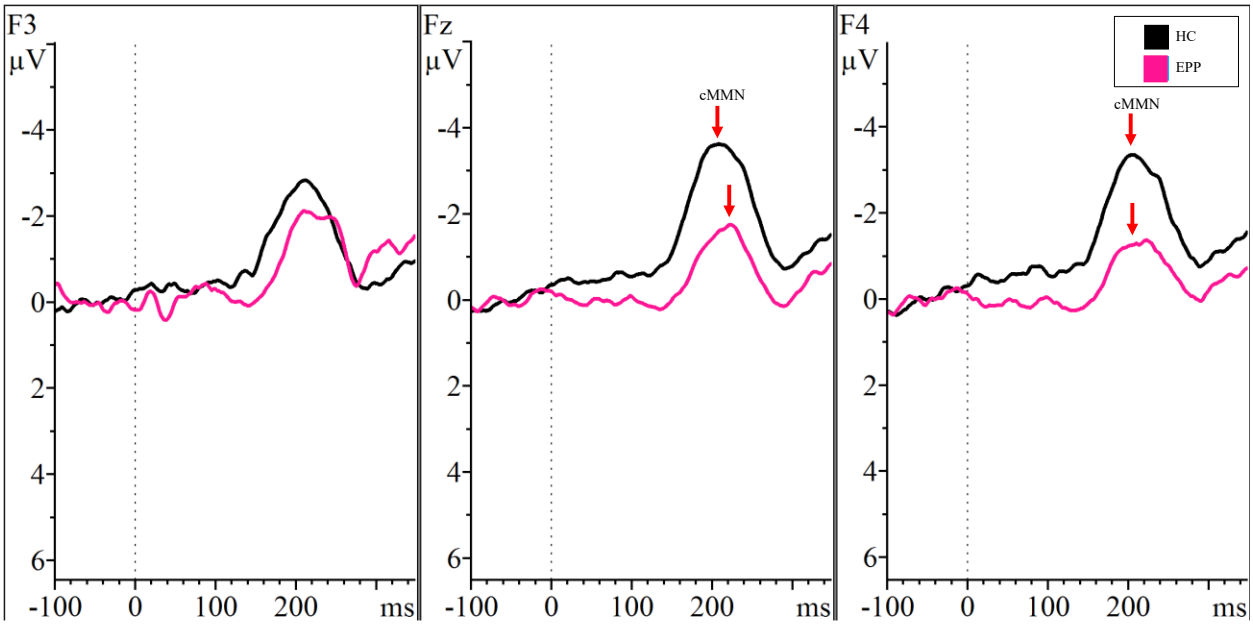
Relationship Between Duration MMN Amplitudes and Social Anhedonia



Note. The above scatterplot demonstrates the significant relationship between MMN amplitudes at electrode site Fz in response to the duration deviant in the optimal multi-feature MMN paradigm and social anhedonia (indicated by scores on the SOPS N1 subscale).

Figure 10.

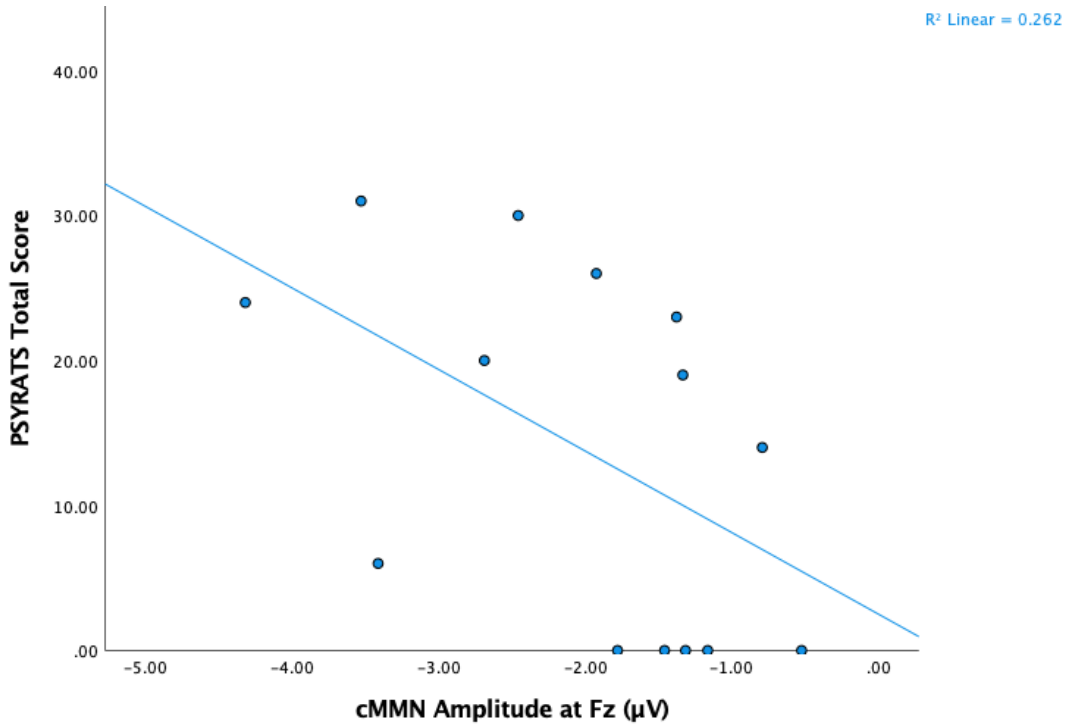
Group Comparison of cMMN Response from Dual Rule Paradigm



Note. The above figure demonstrates the average cMMN amplitudes in the frontal region in response to the deviant tone in the dual rule cMMN paradigm. The black line represents the healthy control group (HC), and the pink line represents the early phase psychosis group (EPP). Statistically significant different amplitudes ($p < .05$) at F4 and Fz are marked with the red arrow.

Figure 11.

Relationship Between cMMN Amplitudes and Auditory Hallucinations



Note. The above scatterplot demonstrates the significant relationship between cMMN amplitudes at electrode site Fz and auditory hallucinations (indicated by total PSYRATS scores).

Appendix A: Recruitment Advertisement

Healthy controls needed for a research study on brain function

If you are 16 to 26 years of age and have never been diagnosed with a psychiatric or neurological disorder, you may be eligible to participate in a research study investigating brain function in people at risk of developing psychosis.

Each participant will attend a 2-hour visit where they will complete questionnaires and computer-based tasks. Electroencephalography (EEG) will be recorded in order to measure brain function during performance of the computer tasks.

You will be reimbursed for your participation in the study.

Contact Information

If you are interested and want more information please contact the lab of Dr. Derek Fisher at 902.457.6441 or derek.fisher@nshealth.ca.

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Appendix B: Global Assessment of Functioning Scale

GLOBAL ASSESSMENT OF FUNCTIONING

GAF-M: When scoring consider psychological, social, and occupational functioning on a hypothetical continuum of mental health/illness. Do not include impairment in functioning due to physical health (or environmental) limitations.

NO SYMPTOMS: 100 - 91
Superior functioning in a wide range of activities Life's problems never seem to get out of hand Sought out by others because of his or her many positive qualities *A person doing exceptionally well in all areas of life = rating 95-100* *A person doing exceptionally well with minimal stress in one area of life = rating 91-94*
ABSENT OR MINIMAL SYMPTOMS: 90 - 81
Minimal or absent symptoms (e.g. mild anxiety before an examination) Good functioning in all areas and satisfied with life Interested and involved in a wide range of activities Socially effective No more than everyday problems or concerns (e.g. an occasional argument with family members) *A person with no symptoms or everyday problems = rating 88-90* *A person with minimal symptoms or everyday problems = rating 84-87* *A person with minimal symptoms and everyday problems = rating 81-83*
SOME TRANSIENT SYMPTOMS: 80 - 71

Mild symptoms are present, but they are transient and expectable reactions to psychosocial stressors (e.g. difficulty concentrating after family argument) Slight impairment in social, work, or school functioning (e.g. temporarily falling behind in school or work) *A person with EITHER mild symptom(s) OR mild impairment in social, work, or school functioning = rating 78-80* *A person with mild impairment in more than 1 area of social, work, or school functioning = rating 74-77* *A person with BOTH mild symptoms AND slight impairment in social, work, and school functioning = rating 71-73*
SOME PERSISTENT MILD SYMPTOMS: 70 - 61
Mild symptoms are present that are NOT just expectable reactions to psychosocial stressors (e.g. mild or lessened depression and/or mild insomnia) Some persistent difficulty in social, occupational, or school functioning (e.g. occasional truancy, theft within the family, or repeated falling behind in school or work) BUT has some meaningful interpersonal relationships *A person with EITHER mild persistent symptoms OR mild difficulty in social, work, or school functioning = rating 68-70* *A person with mild persistent difficulty in more than 1 area of social, work, or school functioning = rating 64-67* *A person with BOTH mild persistent symptoms AND some difficulty in social, work, and school functioning = rating 61-63*
MODERATE SYMPTOMS: 60 - 51

Moderate symptoms (e.g. frequent, depressed mood and insomnia and/or moderate ruminating and obsessing; or occasional anxiety attacks; or flat affect and circumstantial speech; or eating problems and below minimum safe weight without depression)

Moderate difficulty in social, work, or school functioning (e.g. few friends or conflicts with co-workers)

A person with EITHER moderate symptoms OR moderate difficulty in social, work, or school functioning = rating 58-60

A person with moderate difficulty in more than 1 area of social, work, or school functioning = rating 54-57

A person with BOTH moderate symptoms AND moderate difficulty in social, work, and school functioning = rating 51-53

Global Assessment of Functioning (cont'd)

SOME SERIOUS SYMPTOMS OR IMPAIRMENT IN FUNCTIONING: 50 - 31

Serious impairment with work, school, or housework if a housewife/househusband (e.g. unable to keep a job or stay in school, or failing school, or unable to care for family and house)

Frequent problems with the law (e.g. frequent shoplifting, arrests) or occasional combative behavior

Serious impairment in relationships with friends (e.g. very few or no friends, or avoids what friends s/he has)

Serious impairment in relationships with family (e.g. frequent fights with family and/or neglects family or has no home)

Serious impairment in judgment (including inability to make decisions, confusion, disorientation)

Serious impairment in thinking (including constant preoccupation with thoughts, distorted body image, paranoia)

Serious impairment in mood (including constant depressed mood plus helplessness and hopelessness, or agitation, or manic mood)

Serious impairment due to anxiety (panic attacks, overwhelming anxiety)

Other symptoms: some hallucinations, delusions, or severe obsessional rituals

Passive suicidal ideation

A person with 1 area of disturbance = rating 48-50

A person with 2 areas of disturbance = rating 44-47

A person with 3 areas of disturbance = rating 41-43

A person with 4 areas of disturbance = rating 38-40

A person with 5 areas of disturbance = rating 34-37

A person with 6 areas of disturbance = rating 31-33

INABILITY TO FUNCTION IN ALMOST ALL AREAS: 30 - 21
Suicidal preoccupation or frank suicidal ideation with preparation OR behavior considerably influenced by delusions or hallucinations OR serious impairment in communication (sometimes incoherent, acts grossly inappropriately, or profound stuporous depression) Serious impairment with work, school, or housework if a housewife/househusband (e.g. unable to keep a job or stay in school, or failing school, or unable to care for family and house) Frequent problems with the law (e.g. frequent shoplifting, arrests) or occasional combative behavior Serious impairment in relationships with friends (e.g. very few or no friends, or avoids what friends s/he has) Serious impairment in relationships with family (e.g. frequent fights with family and/or neglects family or has no home) Serious impairment in judgment (including inability to make decisions, confusion, disorientation) Serious impairment in thinking (including constant preoccupation with thoughts, distorted body image, paranoia) Serious impairment in mood (including constant depressed mood plus helplessness and hopelessness, or agitation, or manic mood) Serious impairment due to anxiety (panic attacks, overwhelming anxiety) Other symptoms: some hallucinations, delusions, or severe obsessional rituals Passive suicidal ideation *A person with any 1 of the first 3 (unique) criteria = rating 21* *OR a person with 7 of the combined criteria = rating 28-30* *A person with 8-9 of the combined criteria = rating 24-27* *A person with 10 of the combined criteria = rating 20-23*

Global Assessment of Functioning (cont'd)

IN SOME DANGER OF HURTING SELF OR OTHERS: 20 - 11
Suicide attempts without clear expectation of death (e.g. mild overdose or scratching wrists with people around) Some severe violence or self-mutilating behaviors Severe manic excitement, or severe agitation and impulsivity Occasionally fails to maintain minimal personal hygiene (e.g. diarrhea due to laxatives, or smearing feces) Urgent/emergency admission to the present psychiatric hospital In physical danger due to medical problems (e.g. severe anorexia or bulimia and some spontaneous vomiting or extensive laxative/diuretic/diet pill use, but without serious heart or kidney problems or severe dehydration and disorientation) *A person with 1-2 of the 6 areas of disturbance in this category = rating 18-20* *A person with 3-4 of the 6 areas of disturbance in this category = rating 14-17* *A person with 5-6 of the 6 areas of disturbance in this category = rating 11-13*
IN PERSISTENT DANGER OF SEVERELY HURTING SELF OR OTHERS: 10 - 1
Serious suicidal act with clear expectation of death (e.g. stabbing, shooting, hanging, or serious overdose, with no one present) Frequent severe violence or self-mutilation Extreme manic excitement, or extreme agitation and impulsivity (e.g. wild screaming and ripping the stuffing out of a bed mattress) Persistent inability to maintain minimal personal hygiene Urgent/emergency admission to present psychiatric hospital In acute, severe danger due to medical problems (e.g. severe anorexia or bulimia with heart/kidney problems, or spontaneous vomiting WHENEVER food is ingested, or severe depression with out-of-control diabetes) *A person with 1-2 of the 6 areas of disturbance in this category = rating 8-10* *A person with 3-4 of the 6 areas of disturbance in this category = rating 4-7* *A person with 5-6 of the 6 areas of disturbance in this category = rating 1-3*

Adapted from: Hall, R. (1995). Global assessment of functioning: A modified scale, *Psychosomatics*, *36*, 267-275.

Current Score: _____ Highest Score in past year:_____

Appendix C: Social and Occupational Functioning Scale

Exhibit 5-6 Social and Occupational Functioning Assessment Scale (SOFAS)

Consider social and occupational functioning on a continuum from excellent functioning to grossly impaired functioning. Include impairments in functioning due to physical limitations, as well as those due to mental impairments. To be counted, impairment must be a direct consequence of mental and physical health problems; the effects of lack of opportunity and other environmental limitations are not to be considered.

91-100	SUPERIOR FUNCTIONING in a wide range of activities.
81-90	GOOD FUNCTIONING in all areas, occupationally and socially effective.
71-80	SLIGHT IMPAIRMENT in social, occupational, or school functioning (e.g. infrequent interpersonal conflict, temporarily falling behind in schoolwork).
61-70	SOME DIFFICULTY in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships.
51-60	MODERATE DIFFICULTY in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers).
41-50	SERIOUS IMPAIRMENT in social, occupational, or school functioning (e.g., no friends, unable to keep a job) *in some areas.*
31-40	MAJOR IMPAIRMENT IN SEVERAL AREAS, such as work or school, family relations (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and failing at school).
21-30	INABILITY TO FUNCTION *socially or occupationally* in almost all areas (e.g., stays in bed all day; no job, home, or friends).
11-20	OCCASIONAL HYGIENE PROBLEMS, fails to maintain minimal personal hygiene; unable to function independently.
1-10	PERSISTENT HYGIENE PROBLEMS, inability to maintain minimal personal hygiene. Unable to function without harming self or others or without considerable external support (e.g. nursing care and supervision).
0	Inadequate information.

Source: *DSM-IV* Axis V (APA, 1994, pp. 760-761) with expansions in italics; see also Goldman, H.H., Skodol, A.E., & Lave, T.R. (1992). Revising Axis X for *DSM-IV*: A review of measures of social functioning. American Journal of Psychiatry, 149, 1148-1156. *(NOTE: Italics added to make it more specific and delineate ratings more.)*

Appendix D: Scale of Prodromal Sympotoms

P. POSITIVE SYMPTOMS

P. 1. UNUSUAL THOUGHT CONTENT/DELUSIONAL IDEAS

The following questions are organized in sections and probe for both psychotic, delusional thinking and for non-psychotic, unusual thought content.
These experiences are rated on the SOPS P1 Scale at the end of the queries.

Y=YESN=NO NI=NO INFORMATION

PERPLEXITY AND DELUSIONAL MOOD

INQUIRY:

1. **Have you had the feeling that something odd is going on or that something is wrong that you can't explain?**
   N NI Y (Record Qualifiers)
2. **Have you ever been confused at times whether something you have experienced is real or imaginary?**
   N NI Y (Record Qualifiers)
3. **Do familiar people or surroundings ever seem strange?** Confusing? Unreal? Not a part of the living world? Alien? Inhuman? Evil?
   N NI Y (Record Qualifiers)
4. **Does your experience of time seem to have changed? Unnaturally faster, unnaturally slower?**
   N NI Y (Record Qualifiers)
5. **Do you ever seem to live through events exactly as you have experienced them before?**
   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

FIRST RANK SYMPTOMS

INQUIRY:

1. **Have you felt that you are not in control of your own ideas or thoughts?**
   N NI Y (Record Qualifiers)
2. **Do you ever feel as if somehow thoughts are put into your head or taken away from you?** Do you ever feel that some person or force may be controlling or interfering with your thinking?
   N NI Y (Record Qualifiers)
3. **Do you ever feel as if your thoughts are being said out loud so that other people can hear them?**
   N NI Y (Record Qualifiers)
4. **Do you ever think that people might be able to read your mind?**
   N NI Y (Record Qualifiers)
5. **Do you ever think that you can read other people's minds?**
   N NI Y (Record Qualifiers)
6. **Do you ever feel the radio or TV is communicating directly to you?**
   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

OVERVALUED BELIEFS

INQUIRY:

1. **Do you have strong feelings or beliefs that are very important to you, about such things as religion, philosophy, or politics?**
   N NI Y (Record Qualifiers)
2. **Do you daydream a lot or find yourself preoccupied with stories, fantasies, or ideas?** Do you ever feel confused about whether something is your

imagination or real?

N NI Y (Record Qualifiers)

3. **Do you know what it means to be superstitious? Are you superstitious? Does it affect your behavior?**
   N NI Y (Record Qualifiers)
4. **Do other people tell you that your ideas or beliefs are unusual or bizarre? N NI Y (Record Qualifiers)**
   If so, what are these ideas or beliefs?
5. **Do you ever feel you can predict the future?**
   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

OTHER UNUSUAL THOUGHTS/DELUSIONAL IDEAS

INQUIRY:

1. **Somatic Ideas: Do you ever worry that something might be wrong with your body or your health?**

   N NI Y (Record Qualifiers)

2. **Nihilistic Ideas: Have you ever felt that you might not actually exist?**
   Do you ever think that the world might not exist?

   N NI Y (Record Qualifiers)

3. **Ideas of Guilt: Do you ever find yourself thinking a lot about how to be good or begin to believe that you deserve to be punished in some way?**

   N NI Y (Record Qualifiers)

NON-PERSECUTORY IDEAS OF REFERENCE

INQUIRY:

1. **Have you felt that things happening around you have a special meaning for just you?**

   N NI Y (Record Qualifiers)

2. **Have you had the sense that you are often the center of people's attention?**
   Do you feel they have hostile or negative intentions?

   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

P. 1. DESCRIPTION: UNUSUAL THOUGHT CONTENT/DELUSIONAL IDEAS

a. Perplexity and delusional mood. Mind tricks, such as the sense that something odd is going on or puzzlement and confusion about what is real or imaginary. The familiar feels strange, confusing, ominous, threatening, or has special meaning. Sense that self, others, the world have changed. Changes in perception of time. Déjà vu experience.
b. Non-persecutory ideas of reference.
c. First rank phenomenology. Mental events such as thought insertion/interference/withdrawal/broadcasting/ telepathy/external control/radio and TV messages.
d. Overvalued beliefs. Preoccupation with unusually valued ideas (religion, meditation, philosophy, existential themes). Magical thinking that influences behavior and is inconsistent with subculture norms (e.g. being superstitious, belief in clairvoyance, uncommon religious beliefs).
e. Unusual ideas about the body, guilt, nihilism, jealousy and religion. Delusions may be present but are not well organized and not tenaciously held.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

UNUSUAL THOUGHT CONTENT/DELUSIONAL IDEAS **Severity Scale (circle one)**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe but Not Psychotic	6 Severe and Psychotic
	"Mind tricks" that are puzzling. Sense that something is different.	Overly interested in fantasy life. Unusually valued ideas/beliefs. Some superstitions beyond what might be expected by the average person but within cultural norms.	Unanticipated mental events that are puzzling, unwilled, but not easily ignored. Experiences seem meaningful because they recur and will not go away. Functions mostly as usual.	Sense that ideas/experiences /beliefs may be coming from outside oneself or that they may be real, but doubt remains intact. Distracting, bothersome. May affect functioning.	Experiences familiar, anticipated. Doubt can be induced by contrary evidence and others' opinions. Distressingly real. Affects daily functioning.	Delusional conviction (with no doubt) at least intermittently. Interferes persistently with thinking, feeling, social relations, and/or behavior.

Rating based on:_____

For Symptoms Rated at Level 3 or Higher			
Symptom Onset	**Symptom Worsening**	**Symptom Frequency**	**Better Explained**
Record date when a positive symptom first reached at least a 3: ☐ "Ever since I can recall" ☐ Date of onset ___/___ Month/Year	Record most recent date when a positive symptom currently rated 3-6 experienced an increase by at least one rating point: Date of worsening ___/___ Month/Year	Check all that apply: ☐ ≥ 1h/d, ≥ 4d/wk ☐ ≥ several minutes/d, ≥ 1x/mo ☐ ≥ 1x/wk ☐ none of above	Symptoms are better explained by another Axis I or II disorder. Check one: ☐ Likely ☐ Not likely

P. 2. SUSPICIOUSNESS/PERSECUTORY IDEAS

The following questions probe for paranoid ideas of reference, paranoid thinking or suspiciousness. They
are rated on the SOPS P2 Scale at the end of the queries.

SUSPICIOUSNESS/PERSECUTORY IDEAS

INQUIRY:

1. **Do you ever feel that people around you are thinking about you in a negative way?**
   Have you ever found out later that this was not true or that your suspicions were unfounded?
   N NI Y

(Record Qualifiers)

2. **Have you ever found yourself feeling mistrustful or suspicious of other people? N NI Y (Record Qualifiers)**
3. **Do you ever feel that you have to pay close attention to what's going on around you in order to feel safe?**
   N NI Y (Record Qualifiers)
4. **Do you ever feel like you are being singled out or watched?**
   N NI Y (Record Qualifiers)
5. **Do you ever feel people might be intending to harm you?** Do you have a sense of who that might be?
   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

P.2 DESCRIPTION: SUSPICIOUSNESS/PERSECUTORY IDEAS

a. Persecutory ideas of reference.
b. Suspiciousness or paranoid thinking.
c. Presents a guarded or even openly distrustful attitude that may reflect delusional conviction and intrude on the interview and/or behavior.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

SUSPICIOUSNESS/PERSECUTORY IDEAS **Severity Scale (circle one)**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe but Not Psychotic	6 Severe and Psychotic
	Wariness.	Concerns about safety. Hypervigil-ance without clear source of danger.	Concerns that people are untrustworthy and/or may harbor ill will. Sense of unease and need for vigilance (often unfocused). Mistrustful. Recurrent (yet unfounded) sense that people might be thinking or saying negative things about person..	Thoughts of being the object of negative attention. Sense that people may wish harm. Self-generated skepticism present. Preoccupying, distressing. May affect daily functioning. May appear defensive in response to questioning.	Beliefs about danger from hostile intentions of others. Skepticism and perspective can prevail with non-confirming evidence or other's opinion. Anxious, unsettled. Daily functioning affected. Guarded presentation may diminish information gathered in the interview.	Delusional paranoid conviction (no doubt) at least intermittently. Frightened, avoidant, watchful. Interferes persistently with thinking, feeling, social relations, and/or behavior.

Rating based on: _____

_____

_____

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For Symptoms Rated at Level 3 or Higher			
Symptom Onset	**Symptom Worsening**	**Symptom Frequency**	**Better Explained**
Record date when a positive symptom first reached at least a 3: ☐ "Ever since I can recall" ☐ Date of onset ___/___ Month/Year	Record most recent date when a positive symptom currently rated 3-6 experienced an increase by at least one rating point: Date of worsening ___/___ Month/Year	Check all that apply: ☐ ≥ 1h/d, ≥ 4d/wk ☐ ≥ several minutes/d, ≥ x/mo ☐ ≥ 1x/wk ☐ none of above	Symptoms are better explained by another Axis I or II disorder. Check one: ☐ Likely ☐ Not likely

P. 3. GRANDIOSE IDEAS

The following questions probe for psychotic grandiosity, non-psychotic grandiosity, and inflated self-esteem. They are rated on the SOPS P3 Scale at the end of the queries.

GRANDIOSE IDEAS

INQUIRY:

1. **Do you feel you have special gifts or talents?** Do you feel as if you are unusually gifted in any particular area? Do you talk about your gifts with other people?

N NI Y

(Record Qualifiers)

2. **Have you ever behaved without regard to painful consequences? For example, do you ever go on excessive spending sprees that you can't afford?** **N NI Y (Record Qualifiers)**
3. **Do people ever tell you that your plans or goals are unrealistic?** What are these plans? How do you imagine accomplishing them?

N NI Y (Record Qualifiers)

4. **Do you ever think of yourself as a famous or particularly important person?** **N NI Y (Record Qualifiers)**
5. **Do you ever feel that you have been chosen by God for a special role?** Do you ever feel as if you can save others?

N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

P.3 DESCRIPTION: GRANDIOSE IDEAS

a. Exaggerated self-opinion and unrealistic sense of superiority.
b. Some expansiveness or boastfulness.
c. Occasional clear-cut grandiose delusions that can influence behavior.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

GRANDIOSE IDEAS **Severity Scale (circle one)**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe but Not Psychotic	6 Severe and Psychotic
	Private thoughts of being better than others.	Mostly private thoughts of being talented, understanding, or gifted.	Notions of being unusually gifted, powerful or special and have exaggerated expectations. May be expansive but can redirect to the everyday on own.	Beliefs of talent, influence, and abilities. Unrealistic goals that may affect plans and functioning, but responsive to other's concerns and limits.	Compelling beliefs of superior intellect, attractiveness, power, or fame. Skepticism and modesty can only be elicited by the efforts of others. Affects functioning.	Delusions of grandiosity with conviction (no doubt) at least intermittently Interferes persistently with thinking, feeling, social relations, or behavior.

Rating based on:

For Symptoms Rated at Level 3 or Higher			
Symptom Onset	**Symptom Worsening**	**Symptom Frequency**	**Better Explained**
Record date when a positive symptom first reached at least a 3: ☐ "Ever since I can recall" ☐ Date of onset ___/___ Month/Year	Record most recent date when a positive symptom currently rated 3-6 experienced an increase by at least one rating point: Date of worsening ___/___ Month/Year	Check all that apply: ☐ ≥ 1h/d, ≥ 4d/wk ☐ ≥ several minutes/d, ≥ 1x/mo ☐ ≥ 1x/wk ☐ none of above	Symptoms are better explained by another Axis I or II disorder. Check one: ☐ Likely ☐ Not likely

P. 4. PERCEPTUAL ABNORMALITIES/HALLUCINATIONS

The following questions probe for both hallucinations and nonpsychotic perceptual abnormalities. They are rated on the SOPS P4 Scale at the end of the queries.

PERCEPTUAL DISTORTIONS, ILLUSIONS, HALLUCINATIONS

INQUIRY:

1. Do you ever feel that your mind is playing tricks on you?
N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

AUDITORY DISTORTIONS, ILLUSIONS, HALLUCINATIONS

INQUIRY:

1. Do you ever feel that your ears are playing tricks on you?
N NI Y (Record Qualifiers)

2. Have you been feeling more sensitive to sounds? Have sounds seemed different? Louder or softer?
N NI Y (Record Qualifiers)

3. Do you ever hear unusual sounds like banging, clicking, hissing, clapping,

ringing in your ears?

N NI Y (Record Qualifiers)

4. Do you ever think you hear sounds and then realize that there is probably nothing there?

N NI Y

(Record Qualifiers)

5. Do you ever hear your own thoughts as if they are being spoken outside your head?

N NI Y

(Record Qualifiers)

6. Do you ever hear a voice that others don't seem to or can't hear? Does it sound clearly like a voice speaking to you as I am now? Could it be your own thoughts or is it clearly a voice speaking out loud?

N NI Y (Record Qualifiers)

VISUAL DISTORTIONS, ILLUSIONS, HALLUCINATIONS

INQUIRY:

1. Do you ever feel your eyes are playing tricks on you?

N NI Y (Record Qualifiers)

2. Do you seem to feel more sensitive to light or do things that you see ever

N NI Y (Record Qualifiers)

appear different in color, brightness or dullness; or have they changed in some other way?

3. Have you ever seen unusual things like flashes, flames, vague figures or

N NI Y (Record Qualifiers)

shadows out of the corner of your eye?

4. Do you ever think you see people, animals, or things, but then realize they

N NI Y (Record Qualifiers)

may not really be there?

5. Do you ever see things that others can't or don't seem to see?

N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

SOMATIC DISTORTIONS, ILLUSIONS, HALLUCINATIONS

INQUIRY:

1. Have you noticed any unusual bodily sensations such as tingling, pulling, pressure, aches, burning, cold, numbness, vibrations, electricity, or pain? N NI Y (Record Qualifiers)

OLFACTORY AND GUSTATORY DISTORTIONS, ILLUSIONS, HALLUCINATIONS

INQUIRY:

1. Do you ever smell or taste things that other people don't notice?
N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

P. 4. DESCRIPTION: PERCEPTUAL ABNORMALITIES/HALLUCINATIONS

a. Unusual perceptual experiences. Heightened or dulled perceptions, vivid sensory experiences, distortions, illusions.

b. Pseudo-hallucinations or hallucinations into which the subject has insight (i.e. is aware of their abnormal nature.)

c. Occasional frank hallucinations that may minimally influence thinking or behavior.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

PERCEPTUAL ABNORMALITIES/HALLUCINATIONS **Severity Scale (circle one)**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe but Not Psychotic	6 Severe and Psychotic
	Minor, but noticeable perceptual sensitivity (e.g. heightened, dulled, distorted, etc.).	Unformed perceptual experiences/ changes that are noticed but not considered to be significant.	Recurrent, unformed, images (e.g., shadows, trails, sounds, etc.), illusions, or persistent perceptual distortions that are puzzling and experienced as unusual.	Illusions or momentary formed hallucinations that are ultimately recognized as unreal yet can be distracting, curious, unsettling. .May affect functioning.	Hallucinations experienced as external to self though skepticism can be induced by others. mesmerizing, distressing. Affects daily functioning.	Hallucinations perceived as real and distinct from the person's thoughts. Skepticism cannot be induced. Captures attention, frightening. Interferes persistently with thinking, feeling, social relations and/or behavior.

Rating based on:

For Symptoms Rated at Level 3 or Higher			
Symptom Onset	**Symptom Worsening**	**Symptom Frequency**	**Better Explained**
Record date when a positive symptom first reached at least a 3: ☐ "Ever since I can recall" ☐ Date of onset ___/___ Month/Year	Record most recent date when a positive symptom currently rated 3-6 experienced an increase by at least one rating point: Date of worsening ___/___ Month/Year	Check all that apply: ☐ ≥ 1h/d, ≥ 4d/wk ☐ ≥ several minutes/d, ≥ 1x/mo ☐ ≥ 1x/wk ☐ none of above	Symptoms are better explained by another Axis I or II disorder. Check one: ☐ Likely ☐ Not likely

P. 5. DISORGANIZED COMMUNICATION

The following questions probe for thought disorder and other difficulties in thinking as reflected in speech. They are rated on the SOPS P5 Scale.

Note: Basis for rating includes: Verbal communication and coherence during the interview as well as reports of problems with speech.

COMMUNICATION DIFFICULTIES

INQUIRY:

1. **Do people ever tell you that they can't understand you? Do people ever seem to have difficulty understanding you?**

   N NI Y (Record Qualifiers)

2. **Are you aware of any ongoing difficulties getting your point across, such as finding yourself rambling or going off track when you talk?**

   N NI Y (Record Qualifiers)

3. **Do you ever completely lose your train of thought or speech, like suddenly blanking out?**

   N NI Y (Record Qualifiers)

QUALIFIERS: For all "Y" responses, record:

- **DESCRIPTION-ONSET-DURATION-FREQUENCY**
- **DEGREE OF DISTRESS: What is this experience like for you? (Does it bother you?)**
- **DEGREE OF INTERFERENCE WITH LIFE: Do you ever act on this experience? Does having the experience ever cause you to do anything differently?**
- **DEGREE OF CONVICTION/MEANING: How do you account for this experience? Do you ever feel that it could just be in your head? Do you think this is real?**

P. 5. DESCRIPTION: DISORGANIZED COMMUNICATION

a. Odd speech. Vague, metaphorical overelaborate, stereotyped.
b. Confused, muddled, racing or slowed down speech, using the wrong words, talking about things irrelevant to context or going off track.
c. Speech is circumstantial, tangential or paralogical. There is some difficulty in directing sentences toward a goal.
d. Loosening or paralysis (blocking) of associations may be present and make speech hard to follow or unintelligible.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

DISORGANIZED COMMUNICATION **Severity Scale (circle one)**

0	1	2	3	4	5	6
Absent	Questionably Present	Mild	Moderate	Moderately Severe	Severe but Not Psychotic	Severe and Psychotic

	Occasional word or phrase doesn't make sense.	Speech that is slightly vague, muddled, overelaborate or stereotyped.	Incorrect words, irrelevant topics. Goes off track, but redirects on own.	Speech is circumstantial (i.e. eventually getting to the point). Difficulty directing sentences toward a goal. Sudden pauses. Can be redirected with occasional questions and structuring.	Speech tangential (i.e. never getting to the point). Some loosening of associations or blocking. Can reorient briefly with frequent prompts or questions.	Communication persistently loose, irrelevant, or blocked and unintelligible when under minimal pressure or when the content of the communication is complex. Not responsive to structuring of the interview.

Rating based on: _____

_____

_____

For Symptoms Rated at Level 3 or Higher			
Symptom Onset	**Symptom Worsening**	**Symptom Frequency**	**Better Explained**
Record date when a positive symptom first reached at least a 3: ☐ "Ever since I can recall" ☐ Date of onset ___/___ Month/Year	Record most recent date when a positive symptom currently rated 3-6 experienced an increase by at least one rating point: Date of worsening ___/___ Month/Year	Check all that apply: ☐ ≥ 1h/d, ≥ 4d/wk ☐ ≥ several minutes/d, ≥ 1x/mo ☐ ≥ 1x/wk ☐ none of above	Symptoms are better explained by another Axis I or II disorder. Check one: ☐ Likely ☐ Not likely

N. NEGATIVE SYMPTOMS

N. 1. SOCIAL ANHEDONIA

INQUIRY:

1. **Do you usually prefer to be alone or with others?** (If prefers to be alone**,**

specify reason.) Social apathy? Ill at ease with others? Anxiety? Other?
Record Response

2. **What do you usually do with your free time?** Would you be more social if you had the opportunity?
Record Response

3. **How often do you spend time with friends outside of school/work?**
Who are your three closest friends? What sorts of activities do you do together? **Record Response**

4. **Who tends to initiate social contact, you or others?**
Record Response

5. **How often do you spend time with family members?** What do you do with them?
Record Response

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME.

N. 1. DESCRIPTION: SOCIAL ANHEDONIA

a. Lack of close friends or confidants other than first degree relatives.
b. Prefers to spend time alone, although participates in social functions when required. Does not initiate contact.
c. Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

SOCIAL ANHEDONIA OR WITHDRAWAL **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme

	Slightly socially awkward but socially active.	Ill at ease with others. Only mildly interested in social situations but socially present.	Participates socially only reluctantly due to disinterest. Passively goes along with social activities	Few friends outside of extended family. Socially apathetic. Minimal social participation	Significant difficulties with relationships or no close friends. Prefers to be alone. Spends most time alone or with first-degree relatives.	No friends. Prefers being alone.

Rating based on: _____

Symptom Onset (for symptoms rated at a level 3 or higher)
Record date when the earliest symptom first occurred: ☐ Entire lifetime or "ever since I can remember" ☐ Cannot be determined ☐ Date of onset _____/_____ Month Year

N. 2. AVOLITION

INQUIRY:

1. **Do you find that you have trouble getting motivated to do things?**
   N NI Y (Record Response)
2. **Are you having a harder time getting normal daily activities done?**
   N NI Y (Record Response)
   Sometimes? Always? Does prodding work? Sometimes? Never?
3. **Do you find that people have to push you to get things done?** Have you stopped doing anything that you usually do?
   N NI Y (Record Response)

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME.

N. 2. DESCRIPTION: AVOLITION

a. Impairment in the initiation, persistence, and control of goal-directed activities.
b. Low drive, energy, or productivity.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

AVOLITION **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme
	Focus on goal-directed activities but less than what would be considered average.	Low drive or energy level. Simple tasks require effort or take longer than what would be considered normal. Productivity is considered average or is within normal limits.	Low levels of motivation to participate in goal-directed activities. Impairment in task initiation and/or persistence. Initiation or task completion requires some prodding.	Minimal levels of motivation to participate in or complete goal-directed activities. Prodding needed regularly.	Lack of drive/energy results in a significantly low level of achievement. Most goal-directed activities relinquished. Prodding is needed all of the time, but may not be successful.	Prodding unsuccessful. Not participating in virtually any goal-directed activities.

Rating based on: _____

_____

_____

Symptom Onset (for symptoms rated at a level 3 or higher)

Record date when the earliest symptom first occurred:
☐ Entire lifetime or "ever since I can remember"
☐ Cannot be determined
☐ Date of onset _____/_____
Month Year

N. 3. EXPRESSION OF EMOTION

INQUIRY:

1. Has anyone pointed out to you that you are less emotional or connected to people than you used to be?

N NI Y (Record Response)

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME.

Note: Basis for rating includes: Observed flattened affect as well as reports of decreased expression of emotions.

N. 3. DESCRIPTION: EXPRESSION OF EMOTION

a. Flat, constricted, diminished emotional responsiveness as characterized by a decrease in expression, modulation of feelings (e.g. monotone speech) and communication gestures (e.g. dull appearance).
b. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication. Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and sustained questions by interviewer.
c. Poor rapport. Lack of interpersonal empathy, openness in conversation, sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and non-verbal communication.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

EXPRESSION OF EMOTION **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme
	Emotional responsiveness slightly delayed or blunted.	Conversation lacks liveliness, feels stilted.	Emotional expression minimal at times but maintains flow of conversation.	Difficulty in sustaining conversation. Speech mostly monotone. Minimal interpersonal empathy. May avoid eye contact.	Starting and maintaining conversation requires direct and sustained questioning by the interviewer. Affect constricted.	Flat affect, monotone speech. Unable to become involved with interviewer or maintain conversation despite active

					Total lack of gestures.	questioning by the interviewer.

Rating based on: _____

_____

_____

Symptom Onset (for symptoms rated at a level 3 or higher)
Record date when the earliest symptom first occurred: ☐ Entire lifetime or "ever since I can remember" ☐ Cannot be determined ☐ Date of onset _____/_____ Month Year

N. 4. EXPERIENCE OF EMOTIONS AND SELF

INQUIRY:

1. **Do your emotions feel less strong in general than they used to?** Do you ever feel numb?

N NI

Y (Record Response)

2. **Do you find yourself having a harder time distinguishing different emotions/feelings?**

N NI Y

(Record Response)

3. **Are you feeling emotionally flat?**

N NI Y (Record Response)

4. **Do you ever feel a loss of sense of self or feel disconnected from yourself or your life?** Like a spectator in your own life?

N NI Y (Record Response)

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME.

_____

_____

N. 4. DESCRIPTION: EXPERIENCE OF EMOTIONS AND SELF

a. Emotional experiences and feelings less recognizable and genuine, appropriate.
b. Sense of distance when talking to others, not feeling rapport with others.
c. Emotions disappearing, difficulty feeling happy or sad.
d. Sense of having no feelings: Anhedonia, apathy, loss of interest, boredom.
e. Feeling profoundly changed, unreal, or strange.
f. Feeling depersonalized, at a distance from self.
g. Loss of sense of self.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

EXPERIENCE OF EMOTIONS AND SELF **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme
	Feeling distant from others. Everyday feelings muted.	Lack of strong emotions or clearly defined feelings.	Emotions feel like they are blunted or not easily distinguishable.	Sense of deadness, flatness or undifferentiated aversive tension. Difficulty feeling emotions, even emotional extremes, (e.g. happy/sad).	Feeling a loss of sense of self. Feeling depersonalized, unreal or strange. May feel disconnected from body, from world, from time. No feelings most of the time.	Feeling profoundly changed and possibly alien to self. No feelings.

Rating based on: _____

_____

Symptom Onset (for symptoms rated at a level 3 or higher)
Record date when the earliest symptom first occurred: ☐ Entire lifetime or "ever since I can remember" ☐ Cannot be determined ☐ Date of onset _____/_____ Month Year

N.5 IDEATIONAL RICHNESS

INQUIRY:

1. Do you sometimes find it hard to understand what people are trying to tell you because you don't understand what they mean?
N NI Y (Record Response)

2. Do people more and more use words you don't understand?
N NI Y (Record Response)

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME

_____

_____

ABSTRACTION QUESTIONS:

Similarities – How are the following alike? **Proverbs – "What does this saying mean?"**

A ball and an orange?_____

_____ a. Don't judge a book by its cover._____

_____

An apple and a banana?_____ _____

_____

_____

A painting and a poem?_____ b. Don't count your chickens before they hatch._____

Air and water?_____

_____

_____

N. 5. DESCRIPTION: IDEATIONAL RICHNESS

a. Unable to make sense of familiar phrases or to grasp the "gist" of a conversation or to follow everyday discourse.
b. Stereotyped verbal content. Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in repetitious, or simple thought content. Some rigidity in attitudes or beliefs. Does not consider alternative positions or has difficulty shifting from one idea to another.
c. Simple words and sentence structure; paucity of dependent clauses or modifications (adjectives/adverbs).
d. Difficulty in abstract thinking. Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks; often utilizes a concrete mode.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

IDEATIONAL RICHNESS **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme
	Some conversa-tional awkwardness.	Trouble grasping nuances of conversation. Diminished conversa-tional give and take.	Correctly interprets most similarities and proverbs. Uses few modifiers (adjectives and adverbs). May miss some abstract comments.	At times misses the "gist" of reasonably uncomplicated conversation. Verbal content may be repetitious and perseverative. Uses simple words and sentence structure without many modifiers. Misses or interprets many similarities and proverbs concretely.	Able to follow and answer simple statements and questions, but has difficulty independently articulating thoughts and experiences. Verbal content restricted and stereotyped. Verbal expression limited to simple, brief sentences. May be unable to interpret most similarities and proverbs.	Unable, at times, to follow any conversation no matter how simple. Verbal content and expression mostly limited to single words and yes/no responses.

Rating based on:_____

_____

_____

Symptom Onset (for symptoms rated at a level 3 or higher)
Record date when the earliest symptom first occurred: ☐ Entire lifetime or "ever since I can remember" ☐ Cannot be determined ☐ Date of onset _____/_____ Month Year

N. 6. OCCUPATIONAL FUNCTIONING

INQUIRY:

1. Does your work take more effort than it used to?
N NI Y (Record Response)

2. Are you having a hard time getting your work done?
N NI Y (Record Response)

3. Have you been doing worse in school or at work? Have you been put on probation or otherwise given notice due to poor performance? Are you failing any classes or considering dropping out of school? Have you ever been "let go" from a job, or are otherwise having trouble keeping a job?

N NI Y (Record Response)

FOR ALL RESPONSES, RECORD: DESCRIPTION, ONSET, DURATION, AND CHANGE OVER TIME.

N. 6. DESCRIPTION: OCCUPATIONAL FUNCTIONING

a. Difficulty performing role functions (e.g. wage earner, student, homemaker) that were previously performed without problems.
b. Having difficulty in productive, instrumental relationships with colleagues at work or school.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

OCCUPATIONAL FUNCTIONING **Negative Symptom Scale**

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe	6 Extreme
	More than average effort and focus required to maintain usual level of performance at work, school.	Difficulty in functioning at work or school that is becoming evident to others.	Definite problems in accomplishing work tasks or a drop in Grade Point Average.	Failing one or more courses. Receiving notice or being on probation at work.	Suspended, failing out of school, or other significant interference with completing requirements. Problematic absence from work. Unable to work with others.	Failed or left school, left employment or was fired.

Rating based on:

Symptom Onset (for symptoms rated at a level 3 or higher)
Record date when the earliest symptom first occurred: ☐ Entire lifetime or "ever since I can remember" ☐ Cannot be determined ☐ Date of onset _____/_____ Month Year

Appendix E: Psychotic Symptoms Rating Scales

PSYCHOTIC SYMPTOM RATING SCALES

A) Auditory hallucinations

1. Frequency

0 Voices not present or present less than once a week
1 Voices occur for at least once a week
2 Voices occur at least once a day
3 Voices occur at least once a hour
4 Voices occur continuously or almost continuously
i.e. stop for only a few seconds or minutes

2. Duration

0 Voices not present
1 Voices last for a few seconds, fleeting voices
2 Voices last for several minutes
3 Voices last for at least one hour
4 Voices last for hours at a time

3. Location

0 No voices present
1 Voices sound like they are inside head only
2 Voices outside the head, but close to ears or head. Voices inside the head may also be present
3 Voices sound like they are inside or close to ears and outside head away from ears
4 Voices sound like they are from outside the head only

4. Loudness

0 Voices not present
1 Quieter than own voice, whispers.
2 About same loudness as own voice
3 Louder than own voice
4 Extremely loud, shouting

5. Beliefs re-origin of voices

0 Voices not present
1 Believes voices to be solely internally generated and related to self
2 Holds!50% conviction that voices originate from external causes
3 Holds&50% conviction (but!100%) that voices originate from external causes
4 Believes voices are solely due to external causes

(100% conviction)

6. Amount of negative content of voices

0 No unpleasant content
1 Occasional unpleasant content (!10%)
2 Minority of voice content is unpleasant or negative
3 Majority of voice content is unpleasant or negative
4 All of voice content is unpleasant or negative

7. Degree of negative content

0 Not unpleasant or negative
1 Some degree of negative content, but not personal comments relating to self or family e.g. swear words or comments not directed to self, e.g. ‘ the milkman’s ugly’
2 Personal verbal abuse, comments on behaviour e.g. ‘ shouldn’t do that or say that’
3 Personal verbal abuse relating to self-concept e.g. ‘ you’re lazy, ugly, mad, perverted’
4 Personal threats to self e.g. threats to harm self or family, extreme instructions or commands to harm self or others

8. Amount of distress

0 Voices not distressing at all
1 Voices occasionally distressing, majority not distressing (!10%)
2 Minority of voices distressing (!50%)
3 Majority of voices distressing, minority not distressing (&50%)
4 Voices always distressing

9. Intensity of distress

0 Voices not distressing at all
1 Voices slightly distressing
2 Voices are distressing to a moderate degree
3 Voices are very distressing, although subject could feel worse
4 Voices are extremely distressing, feel the worst he/she could possibly feel

10. Disruption to life caused by voices

0 No disruption to life, able to maintain social and family relationships (if present)
1 Voices causes minimal amount of disruption to life e.g. interferes with concentration although able to maintain daytime activity and social and

family relationships and be able to maintain independent living without support

2 Voices cause moderate amount of disruption to life causing some disturbance to daytime activity and}or family or social activities. The patient is not in hospital although may live in supported accommodation or receive additional help with daily living skills

3 Voices cause severe disruption to life so that hospitalisation is usually necessary. The patient is able to maintain some daily activities, self-care and relationships while in hospital. The patient may also be in supported accommodation but experiencing severe disruption of life in terms of activities, daily living skills and}or relationships

4 Voices cause complete disruption of daily life requiring hospitalization. The patient is unable to maintain any daily activities and social relationships. Self-care is also severely disrupted.

11. Controllability of voices

0 Subject believes they can have control over the voices and can always bring on or dismiss them at will

1 Subject believes they can have some control over the voices on the majority of occasions

2 Subject believes they can have some control over their voices approximately half of the time

3 Subject believes they can have some control over their voices but only occasionally. The majority of the time the subject experiences voices which are uncontrollable

4 Subject has no control over when the voices occur and cannot dismiss or bring them on at all

Appendix F: Trauma and Life Events Checklist

TALE Checklist

(Trauma And Life Events Checklist, Carr, Hardy & Fornells-Ambrojo, 2018)

This checklist includes a list of common traumatic or stressful life events. We would like to know whether or not you have ever experienced these events and, if so, which has the most impact on you now. If you choose to answer, please just indicate which events you experienced, if they happened more than once, and how old you were when they happened. Thank you.

Have you ever experienced…? (Please see brackets for some examples)	**Yes (✓) or No (×)**	**More than once? Yes (✓)/ No (×)**	**Age(s) -** range if repeated
1. Exposure to war, either in the military or as a civilian? (e.g. combat, ongoing civil unrest, torture, becoming a refugee or political prisoner)			
2. Loss of, or permanent separation from someone close to you such as a parent or caregiver? (e.g. due to death, being placed in care, conflict, divorce)			
3. A period of separation from someone close to you such as a parent or caregiver? (e.g. due to being placed in care, illness, conflict, divorce)			
4. Sudden or unexpected move or change in circumstances? (e.g. changing school, loss of home)			
5. Bullying or harassment at school, work or on the street? (e.g. people saying hurtful things, hitting or shoving)			
6. Discrimination at school, work or on the street? (e.g. being ignored or treated differently)			
7. Someone close to you insulting you, putting you down or humiliating you? (e.g. someone you live with / partner / family member/ caregiver)			
8. Someone close to you being physically violent or aggressive towards you? (e.g. parent / partner, hitting / kicking / throwing things)			
9. Witnessing physical violence or verbal aggression in your home? (e.g. parents fighting, seeing siblings being beaten or hurt)			
10. Someone you did not know being physically violent or aggressive towards you? (e.g. mugging, assault, fight)			
11. Feeling unsafe, unloved or unimportant during childhood? (e.g. no one to look out for you)			
12. Going hungry or thirsty, not having clean clothes or a safe place to stay during childhood?			
13. Someone having any sexual contact with you, before your 16th birthday, that either at the time or looking back on it now was unwanted? (e.g. talking, looking, touching, penetration)			
14. Someone having any sexual contact with you, since your 16th birthday, that either at the time or looking back on it now was unwanted? (e.g. talking, looking, touching, penetration)			
15. Unusual experiences, such as hearing voices, seeing visions or having worries about other people causing you harm, that made you feel in danger or distress?			
16. Acting in ways that put you or someone else in danger or were strange or embarrassing? (e.g. wandering the streets at night, violence, risky sexual behaviours)			
17. Contact with mental health services (e.g. being admitted to hospital) that involved threatening or upsetting events? (e.g. being restrained, coerced, secluded, assaulted, forced to take medicine, or witnessing such events)			
18. Any other contact with health or criminal justice services which was upsetting or frightening?			
19. Any other events that were accidental or did not involve people intending to cause you harm? (e.g. serious illness, accidents, fire, natural disaster)			
20. Apart from the above, has anything else happened in your life that you found distressing? Please specify:			
21a. Do any of the events you have mentioned, <u>that ended at least 1 month ago</u>, still affect you now? Yes / No 21b. Which event or events currently affect you most? Event number(s):			
21c. Overall, how much are you affected now by the event or events select in 21b (from 0 = not at all to 10 = extremely)?			

Carr, Hardy & Fornells-Ambrojo (2018) The Trauma and Life Events (TALE) checklist: Development of a tool for improving routine screening in people with psychosis; *European Journal of Psychotraumatology*

Appendix G: Screening Form

EEG AND PSYCHOSIS RISK STUDY

Screening Questionnaire

Date: _____ ID# :_____

Name: _____ Age: _____ DOB (dd/mm/yyyy): _____

Sex: _____ Education: Grade school 0 1 2 3 4 5 6 7 8
High school 9 10 11 12
Trade/College 13 14
University 13 14 15 16
Master's level 17 18
Ph.D. level 19 20 21

Classification: *CHR / GHR / EPP / HC*

Handedness: *Left / Right* Normal hearing: *Y / N* Vision: *Normal / Corrected*

Telephone: (h) _____ (w) _____ (c)_____

What is your first language? _____ Other languages you are fluent in? _____
Are you employed? Y / N If yes, what is your occupation? _____ F/T or P/T?
If no, why? (retired / disability / let go / by choice)

EXCULSION CRITERIA

- Are you currently on medication on a regular basis for any physical condition? Y / N
- Are you currently using any pain medication on a regular basis? Y / N
- Have you had any steroid use within the past 3 months? Y / N
- Do you have a condition that effects estrogen/progesterone or testosterone levels in your body? Y / N
- Have you ever been diagnosed with a psychiatric or mental illness (e.g. depression, anxiety)? Y / N
  If yes, what disorder was diagnosed? _____
  Are you currently being seen for treatment? _____
  Do you currently receive medication for these illnesses? _____
- Have you ever been diagnosed with a learning disability? Y / N
  If yes, what disorder was diagnosed? _____
- Have you had a head of brain injury in the past 6 months? Y / N
  If yes, did you lose consciousness for one or more hours? _____

To the best of your knowledge:

- Do you have any neurological disorders such as epilepsy, dementia, Parkinson's disease? Y / N

  If yes, which? _____

- What is your daily (or weekly) alcohol consumption? _____

- Have you ever smoked cigarettes? Y / N

  If yes, do you currently smoke? _____

  If no, when did you quit? _____

  How many years have you been a smoker? _____

  How many cigarettes/day? _____

  How long at this rate? _____

- Have you ever used cannabis? Y / N

  If yes, do you currently use it? _____

  - If no, when did you quit? _____

    How many times in your life have you used it? _____
  - If yes, what is the THC/CBD content of your favourite strain? _____

  How many years have you smoked cannabis? _____

  How many times each week do you smoke? _____

- Do you use any street drugs (cocaine, MDMA)? _____

  If yes, What drugs? _____

  How often? _____

FOR FEMALES:

- Do you have a regular menstrual cycle? Y / N
- Do you use oral contraceptives/ have you ever used oral contraceptives in the past 3 months? Y/ N
- Have you ever been pregnant? Y / N