THESIS

DURATION MISMATCH NEGATIVITY IN HIGH-RISK POPULATIONS FOR SCHIZOPHRENIA

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ABSTRACT

DURATION MISMATCH NEGATIVITY IN HIGH-RISK POPULATIONS FOR SCHIZOPHRENIA

Schizophrenia is a potentially disabling and intractable disorder that is categorized by disturbances in sensory information processing and a psychotic episode. Recent research has targeted clinically high-risk populations and used mismatch negativity (MMN) as an identification tool to provide information regarding the onset of psychosis. Patients with schizophrenia have smaller MMNs compared to controls; thus reduced amplitudes may reflect physiological deficits in temporal perception. The present study evaluated differences in duration MMN (dMMN) amplitudes between healthy and potentially high-risk participants. The hypothesis was that the participants who met the criteria for high-risk according to the 16-item Prodromal Questionnaire (PQ) (score > 6) would have attenuated dMMN amplitudes compared to controls. Participants completed the PQ. Brain activity was recorded using EEG while participants were presented with 2880 samples (120 cycles of 24 samples) of randomized tones that differed in duration (Standard = 500 ms; Deviant 1 = 425 ms; Deviant 2 = 250 ms). Three analyses were applied (Analysis 1: Controls = 0; Analysis 2: Traditional cut-off score Controls < 6; Analysis 3: Simple linear regressions). *T*-tests at each electrode location did not yield significance for Deviant 1. Deviant 2 demonstrated significant trends in Analysis 2 (*Fz*: $t(115) = -2.26$, $p = .01$; *Cz*: $t(115) = -2.11$, $p = .02$). Analysis 3 demonstrated a significant negative, linear relationship between survey scores and MMN amplitudes (*Fz*: $R^2 = .034$, $p = .047$). Findings

may provide a tool for identifying those who are considered high-functioning, but could develop psychosis or cognitive and psychological difficulties associated with psychosis.

Keywords: prodromal, schizophrenia, mismatch negativity

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INTRODUCTION

Mismatch Negativity (MMN) is an auditory event-related potential (ERP) that includes presence of a deviant-tone stimulus among frequent standard-tone stimuli. An early negative response waveform is generated approximately 140-210 ms after a stimulus violates the regularity of recent auditory tones. Different domains of MMN are characterized by the way the deviant tone differs from the standard tone, such that the deviant tone must differ in at least one physical feature compared to the standard tones. Examples of domains of MMN or auditory elements that can be manipulated are the following: frequency (fMMN), duration (dMMN), pitch, speech/vowels, and pseudowords sounds. One type of MMN that has gained increasing interest over the last two decades is the dMMN. Duration MMN deficits have been identified in a host of clinical disorders and have been linked to cognitive deficits in clinical populations and older adults (Davalos, Kisley, & Freedman, 2005).

Overall studies, independent of the specific auditory element that is manipulated, have determined that MMN is an index of auditory sensory or echoic memory, context-dependent information processing primarily at the level of auditory cortices, and sound discrimination accuracy (Kujala, Tervaniemi, & Schroger, 2006; Niznikiewicz, Spencer, Dicky, Voglmaier, Seidman, 2009; Shenton, & McCarley, 2009; Umbricht & Krljes, 2005). In short, auditory sensory memory trace refers to the encoding processing by which previous sensory stimuli are programmed and later used as a representation for comparison. Thus, MMN reflects the process by which a sequence of stimuli is encoded into sensory memory and then each new sensory stimuli is automatically compared to this trace (Garrido, Kilner, Stephan, & Friston, 2009). This comparison aspect of MMN heavily influences theories of MMN generation and relationships

with timing theory and therefore, both timing theory and sensory memory traces will be discussed in more detail in the sections below.

The sensory memory process that is engaged in the MMN paradigm has also been confirmed to reflect early processing stages and is unique because of the paradigm's passive and undemanding nature (Belger, Yucel, & Donkers, 2012; Murphy, Rawdon, Kelleher, Twomey, Markey, Cannon, & Roche, 2013). Studies have also confirmed that MMN is generated mainly in the absence of attention. Given this belief paired with the fact that MMN is presumed to be primarily generated in the auditory cortex, the paradigm is frequently applied to disorders associated with disturbances in sensory information processes (Javitt, Grochowski, Shelley, & Ritter, 1997; Oades, Wild-Wall, Juran, Sachsse, Oknina, & Röpcke, 2006; Oknina, Wild-Wall, Oades, Juran, Röpcke, Pfueller, & Chen, 2005; Saint-Amour, Sanctis, Molholm, Ritter, & Foxe, 2007).

Due to MMN's involvement in timing and temporal processing, current reports have argued for MMN's application as a potential biomarker in clinical populations (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015; Light & Näätänen, 2013; Nagai et al., 2013). The following sections will outline the support for this particular application by addressing the theories of timing that inform the use of MMN in clinical settings, underlying neural correlates of timing and MMN generation, the general model associated with MMN generation, previous and current theoretical hypotheses that seek to explain MMN, the importance of MMN as a non-attention-driven process as it pertains to clinical studies, and a summary of prior literature examining different domains of MMN, specifically dMMN, in clinical populations.

Theoretical Underpinnings of Timing and Temporal Processing

The concept of time is central for human behavior, cognition, and overall functionality. Without an ability to process time in a linear fashion, individuals would not be able to carry out day to day functions required in today's society. This includes responding to events, sequencing events, and executive functions, such as planning and decision making. Timing is typically broken down into three facets: motor timing, temporal foresight, and time perception. Motor timing requires integration of a motor plan in an organized fashion in order to achieve a desired output or motor response. Temporal foresight is in reference to long time intervals (minutes, hours, days, etc) and best generalizes to higher order cognitive processes, such as planning and inhibition. This facet is most commonly tested using a reward scenario where participants have the option to instantly receive a reward or wait a specified or unknown amount of time in order to receive a larger or better reward (Rubia et al., 1998). Temporal foresight requires participants to analyze costs and benefits of two scenarios and integrate other cognitive mechanisms, such that if the participant chooses to wait the specified time interval, they must be capable of inhibiting the impulse to take an immediate reward (Rubia et al., 1998).

Compared to the longer intervals, which can range from minutes to days, used in temporal foresight, the third facet, time perception or estimation uses intervals that are much smaller in length (milliseconds to minutes). Temporal perception is a passive process that involves cognitive systems in order to accurately make judgements regarding these intervals (Rubia, 2006). To test this facet, participants are typically asked to reproduce or make estimations regarding the length of these intervals.

Deficits in any of these facets of timing will result in abnormal functioning (Rubia, 2006). Populations that demonstrate inaccuracies of short intervals and therefore temporal

perception are also associated with pathologies including, but not limited to: schizophrenia, brain lesions, dyslexia, Parkinson's, depression, (Rubia, 2006). Deficits in motor timing tend to revolve around disorders associated with dopamine deficits like Parkinson's, but have also been found in learning disabilities, such as dyslexia (Rubia, 2006). Personality traits that are linked to substance abuse and addiction, such as impulsiveness, have also been linked to deficits in temporal foresight. The differences and overlaps in pathology across these domains of timing have allowed researchers in this field to narrow down the underlying cognitive processes that most influence timing. These processes that are most commonly observed are memory and attention. For purposes of the present study, the focus of the following sections will be on the relationship between these two cognitive processes and temporal perception

Mechanisms of Timing: Memory. In timing research, memory is assumed to be organized sequentially, or in time order and can be tested by time-tagging models. The two main time-tagging models that address the role of memory in timing are the strength model and the inference model. The strength model focuses heavily on the idea of comparison; thus, in this model a memory trace is placed on a memory, then time perceptions are created by comparing the memory with the strength of its trace. The strength model is evaluated in research settings using a temporal sequence paradigm (Grondin, 2010).

The inference model of memory and timing integrates autobiographical memory with general world knowledge in order to reconstruct time through guesses or inferences. Under this model, the time of an event is inferred using information about relations between the event in question and other events that may inform missing information. If the date and time of an event is known, this event can be used as a reference or comparison in order to determine the date and

time of the event in question (Grondin, 2010). These generalized memory models are discussed later as these are the underpinnings used to inform more comprehensive models of timing.

Mechanisms of Timing: Attention. Models that seek to explain human understanding of timing in reference to attention tend to use the internal clock model. This is a connectionist model concept that also can be referred to as temporal module, temporal processor hypothesis or pacemaker hypothesis. All of these terms refer to the following general model: A pacemaker emits pulses that are accumulated in the counter or accumulator. This counter is purposed to stock subjective time units and the number of pulses determines the perceived length of an interval (see Figure 1). The stream of the pulse from the pacemaker results in a linearly increasing accumulator value. However, if an individual is not dedicating undivided attention to time, a mechanism referred to as the switch or gate is introduced. The switch determines the flow of pulses when attending to time and is therefore associated with attending to duration-onset signals (Grondin, 2010).

The accuracy of estimating time under the pacemaker model is dependent upon the available attentional resources, which is limited and reliant based on task load. This model works under the assumption that a limited pool of attentional resources exists and these resources are allocated based on importance of the task at hand. Therefore when an error occurs in the pacemaker model, this inaccuracy is attributed to attention (Grondin, 2010). For example, if full attention is dedicated to time, the pacemaker emits pulses that are streamed straight into the accumulator. In a typical individual, this should lead to the high accuracy because there are no distractions: the switch mechanism is irrelevant or closed and the accumulator is operating at a

maximum accuracy. Maximum accuracy refers to the most accurately an individual can estimate time when no other distractions are present.

However, if an additional attention-requiring task or stimulus is added to the equation, there is an interruption between the stream of pulses from the pacemaker to the accumulator and the switch mechanism must open. This leads to errors in timing because attention must be divided between counting subjective time units and the additional task or stimulus. Therefore, as more attention is given to time, perceived duration increases, resulting in fewer errors in interval discrimination. As additional tasks are introduced, the number of switch errors is expected to increase due to reallocation of attentional resources. When attention demand is dispersed across tasks, the ability to accurately and precisely count subject time units diminishes in healthy individuals (Grondin, 2010).

Timing Models. The Scalar Expectancy Theory (SET) (Gibbon, 1977; Grondin, 2010) unites these two underlying cognitive processes in order to explain how healthy individuals are able to accurately estimate time (see Figure 2). The first stage of SET adopts the pacemaker model in full and refers to this as the clock stage. The second stage or memory stage is divided based on working and reference memory. This stage works under the assumption that there is a distribution of memory processes between short and long intervals that can be learned and used as a reference. When a single value is introduced as the interval, this value is then compared against the reference value, which already exists in memory. The third and final stage of SET is called the decision stage. The comparator judges the pulse levels that are estimated in working memory against the sample of previous time durations stored in reference memory. The output of the decision stage is a reference value, which Gibbon (1977) outlined as either *yes* or *no*.

Differences in time perception are attributable to changes in operation of clock, memory or decision changes of the system and can be measured using tasks that focus on specific parts of this model (Grondin, 2010; Papageorgiou et al., 2013).

There are many paradigms that seek to isolate the role of attention and/or memory in timing research. These paradigms can be divided into two main types of timing: retrospective and prospective timing. Retrospective timing tends to focus on memory by having participants make time-related judgments after a longer delay interval. In these retrospective timing tasks, the participants are not told that they will be required to make judgments about time in the future. Alternatively in prospective timing tasks, participants are forewarned that they will be asked to make timing judgments in the future and are accompanied by an additional task. Since in prospective timing tasks participants must simultaneously track time and complete a task, these designs are thought to focus on the role of attention in timing.

The underlying mechanism that distinguishes between examining attention and timing versus memory and timing is if the participants are informed that they will need to accurately estimate time. Therefore, the following examples of task can be applied as either a prospective or retrospective timing task. In verbal estimate tasks, participants are presented with a target interval and are asked to provide a verbal estimation of duration in temporal units. Reproduction refers to a target interval with continuous sounds or flashes and participants are asked to recreate the exact interval in length of the sound or flash. A retrospective design would not inform participants that they will make temporal judgments in the future, thus allowing the participant to rely on memory for accurate recall of timing intervals. A prospective design would inform the participant beforehand, and therefore the participant would have to attend to both the task and the time interval in order to achieve highest accuracy (Grondin, 2010; Papageorgiou et al., 2013).

Understanding the different types of timing tasks used to isolate underlying cognitive function is clinically relevant.

Applications of Timing Models. Eagleman (2002, 2008) demonstrated important findings in this line of research by manipulating timing tasks in healthy, neurotypical individuals. Healthy participants were calibrated to a specific time interval based on when a visual stimulus in the form of a flash of light would be presented and instructed to voluntarily press a key each time the flash was viewed. After participants were accustomed to the time-delay, the flashes changed to a slightly shorter interval and researchers manipulated the key automatically to go down before the participants actually pressed the key. The participants began to perceive the flash as occurring before the key press and more importantly, became angered and reported the key to be reading their mind. A formal behavior report was then taken and overall, these healthy participants described low-level symptomology associated with psychosis such as feelings of loss of control of one's own brain and abilities.

Aside from the idea that temporal impairments may lead to psychosis-related symptoms in healthy participants, a notable finding of the Eagleman studies (2002, 2008) was the idea of recalibration. Participant's responses indicated an internal representation of time, which then had to be recalibrated when the delays were shortened. The nervous system presumably has recalibrated its expectation about the normal temporal relationship between actions and sensations to overcome this latency and correctly determine casualty. In sum, Eagleman (2008) suggested that the recalibration may demonstrate a stored version of the interval because without some form of a baseline, a mismatch would not have been elicited. Eagleman (2008) also suggested that the idea of recalibration supports that there are multiple cortical areas responsible

for time representation and thus the single clock theory does not fully explain the mechanisms that underlie time perception.

Since the healthy participants in Eagleman's study (2002) reported symptoms associated with psychosis, other studies have sought to specifically examine populations that experience psychosis, such as patients with schizophrenia. Papagergiou et al. (2013) applied the SET model in order to compare time processing in healthy controls versus patients with chronic schizophrenia and furthermore, demonstrated that pathology was related to reduced performance on timing tasks. This study used an interval discrimination task where participants were asked to categorize each new stimuli as either equal, shorter, or longer than the comparison tone. The second task was a pacing-replication task where participants had to reproduce a tapping sequence with two different delays: 1 minute and 6 minutes after the target sequence was heard. In this task, healthy participants were able to listen to the tapping sequence, encode the sequence into working memory, and correctly reproduce it one minute after then replicate the target sequence again 6 minutes after. The patients, however, incorporated the tapping sequence, reproduced it incorrectly in the 1 minute condition. In the 6 minute condition, patients reproduced the target sequence with decreased precision and accuracy again. The tendency was that patients would reproduce the target sequence too rapidly compared to controls (Papagergiou et al., 2013).

If patients demonstrated differences between the first and second task, this would be attributed to errors in the clock stage. Since errors existed in the reproduction, the inaccuracy is more likely to be attributed to the memory and decision stages of SET. Deficits may be also specifically in the comparator at the decision stage since, Papagergiou et al. (2013) reported that patients showed deficits in interval discrimination task and therefore, these deficits correlate to higher psychopathy. Thus, understanding the mechanisms that underlie subjective time

estimations has clinical relevance; performance in timing tasks has an inverse relationship with clinical disorders, such that decreased temporal processing abilities were associated with increased clinical pathology.

Neural Correlates of Timing. The structures most commonly attributed to time estimation, discrimination, and reproduction are the following: the frontal lobes, prefrontal cortex (PFC), dorsolateral prefrontal cortex (DLPFC), the anterior cingulate gyrus (ACG), the cerebellum, and the basal ganglia. The roles of each of these regions differ based on the timing task and the interval duration used in that task. Time intervals in the millisecond range are considered short time intervals. These intervals are related to early information processing stages where conscious perception and cognitive processes are unrelated. As previously discussed, the cognitive processes that are relevant in timing tasks are working memory and sustained attention because these processes underlie timing theories. Thus tasks that utilize longer intervals, in the seconds to minutes range, examine the relationship between structures associated with working memory and sustained attention and timing (Rubia, 2006).

Frontal Lobes: A structural division exists in the PFC, which determines the relationship between region and length of time interval. Within the frontal lobes, the PFC has been found active in both short and long intervals, but plays a larger, more crucial role in long interval timing. This effect has been confirmed in lesion studies, where patients with lesions to the PFC demonstrated deficits in long interval time estimation tasks. When lesions were localized to the right side of the DLPFC, time discrimination and estimation task showed impairments up to intervals of several seconds (Rubia, 2006). Also within the PFC, the lateral segments were more related to providing accurate time estimations and discriminations of long intervals as opposed to

short intervals (Rubia, 2006). Lateral regions of the DLPFC have also demonstrated more activation in longer intervals.

Other regions within the PFC have also been confirmed to be associated with long interval tasks. Along with the right side of the DLPFC, the right inferior PFC has shown activation in a large quantity of task (temporal discrimination, attentional-timing tasks, perception of rhythm, reproduction etc.; Rubia, 2006). In temporal discrimination tasks, the anterior cingulate gyrus (ACG) has shown increased activation contiguous with the right inferior frontal cortex (IFC). Furthermore, the IFC alone is thought to maintain perception of time estimation as well. Rubia (2006) supported these findings in a review of fMRI studies that used ERP paradigms in order to examine the structural relationship to timing in the frontal cortex.

Supporting evidence suggests that different areas within the PFC (DLPFC, IFC, ACG) may correlate to the different stages in timing theory. Due to the association with longer intervals and therefore, working memory and sustained attention, it would be logical to associate these regions with stages of the SET that utilize these cognitive processes. Attention is related to first stage in the SET model and validates why these PFC regions may be active in a wide range of time intervals. However, the DLPFC probably contributes most to the second stage of the SET that involves working memory. This view includes a mechanism that holds temporal information in working memory and uses this information as a reference or template for incoming stimuli. As new temporal information is perceived, they are continuously compared to this reference and in order to ultimately make accurate time estimations.

As the SET describes, incoming stimuli are compared in working memory then a decision about this comparison must be made by a comparator (Stage 3). The ACG has been noted as retaining similar function that mimic the comparator role. This in part is due to the ACG's role in

attention and executive control, which are both cognitive processes that are required for an accurate estimation of time. Additionally, this is due to the interconnection between the ACG and PFC (Rubia, 2006). This pathway seems to be attributed to executive functioning (i.e. self-monitoring functions of cognitive control; Rubia, 2006) and therefore has been generalized to play the comparator role in the comparison and decision making stages of the SET model.

Cerebellum: The DLPFC receives projections from the cerebellum. Since these regions are highly connected, certain regions of the cerebellum are thought to play a role in timing tasks. Traditionally, the role of the cerebellum in timing literature is more relevant for motor-timing; however, a medial-lateral structural division exists and gives rise to an important functional distinction. The medial regions of the cerebellum serve as mediators for motor control whereas the lateral regions have demonstrated a notable role in time discrimination tasks and therefore have been generalized to timing theory.

Rubia (2006) reviewed the literature addressing cerebellar activity in timing tasks and evidence suggested that activity exists in both short and long duration intervals. Effects of cerebellar activity during discrimination tasks have been confirmed in examining patients with cerebellar deficits. These patients exhibited significantly reduced accuracy in discriminating both short and long intervals. Rubia (2006) addressed an important distinguishing factor between cerebellar patients and PFC lesion patients: The patients with PFC lesions were successful in improving temporal discrimination deficits with training; however, the patients demonstrated cerebellar deficits were not able to show the same progress.

In healthy patients, cerebellar activity in discrimination tasks is more localized to the lateral regions of the cerebellum. This has been attributed to understanding time on a continuum

in order to make judgments of when events occurred within this continuum. An understanding of temporal occurrence of events may point to an ability to also predict a stimulus. If a stimulus represents an event within a time continuum, then in this case the lateral cerebellum would be attributed to perception of when the stimuli occurred in time. This important role of the cerebellum has led to belief that lateral regions of this structure may also play a role in the internal clock hypothesis (Ivry, Keele, & Diener, 1988).

In reference to the internal clock hypothesis, the cerebellum play a role in both short and long intervals. Ivry et al. (1988) suggested that in long interval tasks, the cerebellum's role more closely resembles the accumulator component of the internal clock. However, the cerebellum also responds to short intervals. Thus, research suggests that this structure presents a more complete functional association to the various features that comprise the internal clock hypothesis.

Basal Ganglia and Other Structures: Like the cerebellum, the basal ganglia also demonstrate activation during both short and long intervals, which also makes this structure a potential neural correlate to the different aspects of the internal clock hypothesis. Rubia (2006) noted that due to the connection via the fronto-striatal and fronto-cerebellar pathways between inferior parietal lobes and each of the regions previously mentioned, it is logical that research aiming to address neural correlates of timing would also examine this regions. However, fMRI studies tend to find limited to no parietal lobe activation and thus, the parietal lobes have been discussed as supporting structures for time estimation (Rubia, 2006). Lesion and fMRI studies have shown that the caudate and putamen of the basal ganglia demonstrate a role in short time intervals in milliseconds (hundreds). Additionally, activation in these regions have been shown

in both time estimation and reproduction tasks in short and long intervals, respectively; however, the basal ganglia is thought to play a slightly more crucial role in short interval timing procedures. In part, this is due to the fact that the putamen is specifically involved in short interval temporal discrimination compared to the rest of the basal ganglia.

Underlying Mechanisms of MMN

There are two main hypotheses that seek to explain the neurophysiological mechanisms that underlie MMN elicitation: the model-adjustment hypothesis and the adaptation hypothesis (Garrido et al., 2009). The adaptation hypothesis argues against MMN as a viable tool and states that generation is caused by a short-lived adaptation, not a sensory memory trace. Furthermore, the adaptation hypothesis suggests that MMN is generated with one neuronal population as opposed to two (Garrido et al., 2009; Jaaskelainen et al., 2004). After approximately 28 minutes, the MMN effect is thought to habituate (Näätänen, 1984). The adaptation hypothesis explains this in stating that the one, local neuronal population adapts to the stimuli and therefore, MMN is not an independent component, but rather a delayed N1 response and explains the second component of MMN as an erroneous interpretation of random activation.

The N100 or N1 component is a negative-going evoked potential that is thought to be reflective of early preattentive functions. The common misconception that MMN is actually a delayed N1 response is primarily due to the fact that these components occur close in time, are both negative, and are both reflective of early information processing stages. However, the important difference between these components is the N100 depends upon unpredictability of a stimulus; such that the N100 can be manipulated or made stronger, demonstrated by a more negative amplitude, when stimuli are random. In contrast, the N100 can become attenuated when

stimuli are repetitive. Additionally, MMN component can be distinguished from the N100 component because MMN elicitation can occur in the absence of the N100 component. Discrimination between N1 and MMN has been shown in studies examining children. The N1 component does not typically develop in children until close to late adolescence whereas MMN can be elicited in newborns (Näätänen, Paavilainen, Rinne, & Alho, 2007). These commonalities between the N1 component and MMN originally supported the adaptation hypothesis, but now offer substantial support against the adaptation hypothesis because research has demonstrated that these components are distinguishable from one another.

The adaptation hypothesis has other criticisms as well. In order for one neuronal population to be sufficient for MMN response, MMN duration and latency would have to match the N1 component. Research using equivalent current dipole modeling has revealed that the temporal source that underlies MMN is most likely located more anterior than the source underlying the N1 component (Garrido et al., 2009). Other support for the role of multiple neuronal populations can be found in studies that have examined NMDA antagonists on MMN responses. Ketamine is the most commonly studied NMDA antagonist in MMN research and there is converging evidence that ketamine blocks MMN generation while having no effect on activity in the auditory cortex, suggesting that a frontal neuronal population must also maintains a role in MMN generation (Garrido et al., 2009; Jaaskelainen et al., 2004).

The model-adjustment hypothesis opposes the adaptation hypothesis in support of MMN's clinical applications. This hypothesis refers to an online model that continuously updates and creates predictions about the next auditory input using previous auditory information (Garrido, Friston, Kiebel, Stephan, Baldeweg, Kilner, 2008; Näätänen & Winkler, 1999; Sussman & Winkler, 2001; Winkler, Karmos, & Näätänen, 1996). This perceptual model

suggests that MMN is generated by a temporal-frontal cortical network and argues for two subcomponents of MMN.

According to the model-adjustment hypothesis, there are two intracranial processes that play a role in elicitation of these subcomponents. The early or first subcomponent is thought to be generated in temporal areas, most likely the superior temporal gyrus approximately 90-120 ms after the deviant tone. The first intracranial process responsible is a bilateral supratemporal process. Evidence for the localization of this subcomponent to the primary auditory cortex is found from mastoid recordings in EEG research. During the MMN paradigm, mastoid recordings demonstrates an inverted polarity compared to the typical negative-going MMN ERP recorded at other electrodes (Garrido et al., 2009). Also, the supratemporal subcomponent is thought to be reflective of pre-perceptual change detection (Näätänen et al., 2007).

The second intracranial process outlined in this model is produced in frontal areas, specifically in the inferior frontal gyrus and predominantly in the right hemisphere. This component arises in approximately the 140-170 ms range. This later or second component is thought to reflect a reorientation of attention due to the deviant tone. Additionally, the prefrontal cortex may also play a role as a top-down modulator for deviance detection in temporal cortices (Garrdio et al, 2009).

The stronger aspects of both the model-adjustment hypothesis and adaptation hypothesis have been merged under the predictive coding or hierarchical inference perspective (Garrido et al., 2009). In reference to previously mentioned models of sensory memory, the predictive coding approach suggests that MMN elicitation depends on both the representation of single auditory elements, which corresponds to the first phase of auditory sensory memory in the Cowan (1984) and Massaro (1970) models and updates based on a sensory memory trace which

corresponds with the second phase of the auditory sensory memory store. Predictive coding views the brain as a system organized by hierarchical levels, where each level receives and integrates input from both the level that precedes and succeeds it. In reference to MMN, each level receives bottom-up information from the level below and top-down information from the level above and the current level must integrate this information to make accurate predictions about incoming sensory information. Therefore, MMN would be the result of an incongruity between top-down prediction and the actual incoming bottom-up sensory information where incoming information from the upper levels is continuously compared to the information. MMN is not continuously elicited after the initial mismatch because the online updates adapt to the repetition and suppress the prediction error (Garrido et al., 2009; Friston, 2005; Baldeweg, Wong, & Stephan, 2006).

MMN Generation

MMN is an EEG paradigm that is habitually used to assess temporal processing, specifically in clinical populations. In order to support MMN's application in clinical populations, a general model and theoretical background of MMN elicitation must first be explained: (1) incoming auditory information enters the ears (2) sensory information is organized based on physical characteristics of the sounds (3) a sound context is developed from the grouping sequence (4) sound elements are segregated or integrated as auditory information continues to enter the ears (5) a response to the standard stimuli is formed (6) incoming sound elements are compared to the established standards (7) an incoming sound element deviates in at least one physical feature from the expected standard sound (8) the deviant is detected (deviance

detection) and (9) an MMN waveform is created by subtracting the averaged response to a set of standard stimuli from the averaged response to a deviant stimuli (Sussman, 2007).

In the model above, standard formation is the first crucial element of MMN elicitation (Sussman, 2007). The term standard refers to the neural representation of the baseline that becomes encoded as a sensory memory and used as a comparison when a deviant tone is presented. A deviant tone must consist of at least one feature value that differs from the standard (e.g. Duration, frequency, etc.). Most findings in the literature agree that randomization of the deviant tone is important for MMN elicitation. If the presentation of the deviant tone consistently follows a pattern, the tone may become incorporated into the pattern sequence instead of being correctly detected as a deviant (as cited in Sussman, 2007).

One of the key questions that emerge is determining which attributes are most critical in an MMN paradigm in order to elicit the MMN waveform. The standard tone in an MMN sequence is a crucial element for deviance detection. Without the standard tone, there would be no comparison attribute and MMN could not be elicited. This idea of a comparison refers to the generation of a sensory memory trace (stage 6). Sensory memory traces are crucial for accurate language acquisition, linguistic processing, auditory processing, and cognitive ability (Atkinson & Shiffrin, 1968; Bartha-Doering, Deuster, Giordano, Zehnhoff-Dinnesen, Dobel, 2015; Cowan, 1984; Massaro, 1970). These traces were first demonstrated in the Atkinson and Shiffrin (1968) model. This model had three stages of memory: sensory registration, short-term store, and long-term store. The sensory registration referred to the store that detects the incoming information and holds the information for a short amount of time. This stage is thought to be pre-attentive and integrate over time and therefore, refers to the current termed sensory memory trace.

Massaro (1970) and Cowan (1984) built off the Atkinson and Shiffrin (1968) model and referred to only two kinds of sensory memory: short and long. The short phase referred to a perceptual store whereas the long phase referred to a synthesized store. Like the sensory registration of the Atkinson and Shiffrin (1968), the short phase is thought to be a pre-attentive phase that also integrates incoming information in a sliding time window (100-300ms). The long phase holds information for 10-20 seconds and integrates over time in one of two ways: Loudness summation and backwards masking. Loudness summation refers to volume added and backwards masking refers to newer sounds succeeding older sounds. Due to the involvement of a sensory memory trace, MMN is thought to be an index of auditory sensory or echoic memory, context-dependent information processing at the primary level of auditory cortices, and sound discrimination accuracy (Kujala et al., 2006; Niznikiewicz, Spencer, Dicky, Voglmaier, Seidman, Shenton, & McCarley, 2009; Umbricht & Krljes, 2005).

Attention, Other ERP Components, and MMN

Attentional deficits are common in various clinical disorders and especially in disorders that relate to sensory memory. Since MMN is thought to be relatively independent of attention, MMN is frequently applied to isolate temporal function in these populations. Thus the relationship between MMN and attention must be addressed. Supporting evidence against MMN as independent of attention refers to the idea that standard formation may be an attention-driven process. This misconception is attributed to an initial attention switch mechanism when the paradigm is first presented (i.e. standard formation, stages 1-5 in the above general model). However, attending to changes in auditory stimuli during the standard formation stages may be indicative of an acoustic reflex. Reflexes can be modulated by cortical influence but do not

require cortical influence and therefore, standard formation remains pre-attentive. Arguments stating that attention is a modulator of MMN are strictly lacking after standard formation is encoded as a sensory memory trace.

MMN can be successfully elicited independent of attention to the stimuli. This effect has been validated in studies examining patients in comas, sleep, and in infants (Garrido et al., 2009; Sallinen, Kaartinen, & Lyytinen, 1994). In tasks where conscious, healthy, participants receive instructions to attend to specified stimuli, an attenuation or influence on the resulting MMN output remains unaffected (Garrido et al., 2009). Therefore, MMN is considered to be resistant to attentional influences and demonstrates the nonconscious manner in which complex comparisons are made at a cortical level (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001).

Additionally, the same, previously discussed arguments that are made about the relationship between N1 and MMN are made about the relationship between the N2b component and MMN. N2b or N200 is also a negative-going evoked potential and is commonly examined in language processing and production settings. Specific MMN researchers use a paradigm where pseudospeech or vowel sounds are used as the standard and deviant tones instead of tones or beeping. In these cases, researchers have to carefully differentiate between the two components in order to correctly identify an effect.

There are studies that have included a behavioral task in order to evaluate MMN's relationship with attention and findings instead demonstrated that by diverting attention away from the MMN paradigm, the MMN ERP waveform can be better distinguished from other ERP components (Näätänen et al., 2007). The Sussman, Winkler, and Schröger (2003) study used predictable and unpredictable conditions to elicit MMN and N2b components. The predictable condition consisted of informing the participant that a visual cue would appear prior to the

deviant tone. The unpredictable condition also used visual cues, but did not inform the participant why they were present. There was no difference in MMN peak amplitude or latency between conditions, suggesting that prior knowledge or expectation that a deviant would occur did not have an effect on MMN. This study further delved into the issue of attention and MMN by addressing the issue of attention-switching in MMN studies. There are arguments that because the P3a component can be elicited in MMN studies, attention still plays a role in MMN elicitation. The P3a component is reflective of attention-switching to a salient auditory stimulus. In the same Sussman et al. (2003) study, the predictable condition eliminated P3a elicitation by inducing expectation and therefore making the deviant tones a relatively familiar auditory tone. Sussman et al. (2003) findings suggested that the expectation of a deviant tone removed the involuntary re-orientation of attention and allowed to parse out the MMN waveform from other components.

Sussman, Winkler, Huotilainen, Ritter, and Näätänen (2002) used slow paced MMN with a single tone or a five-tone pattern to further explore the relationship between standard formation and attention. Researchers instructed participants to attend to specific features of the tone sequence, specifically for the deviant. Results determined that attention did not impact MMN elicitation in the single tone condition; however when the number of tones in the standard sequence increased, findings demonstrated a minimal effect of attention. Sussman (2007) noted that these results may point to an attentional influence on organizing attributes about the patterns, which constituted a standard sequence. Findings demonstrated that at minimum, attention may play a role in standard formation, but this effect is not large enough to influence the final MMN output.

Clinical Applications

Since studies have determined that MMN is an index of auditory sensory memory and is presumed to be primarily generated in the auditory cortex, the paradigm can be applied to disorders associated with disturbances in sensory information processes (Oades et al., 2006; Saint-Amour et al., 2007). Schizophrenia, is one of the clinical disorders that has been historically categorized by disturbances in sensory information processing and temporal dysfunction and therefore, has the most robust findings in MMN research. Shelley, Ward, Catts, Michie, Andrews, and McConaghy (1991) were the first to report reductions in MMN amplitudes in schizophrenia populations. This finding has been confirmed in a meta-analysis by Umbricht and Krljes (2005), which examined the relationship between MMN and schizophrenia across approximately 40 studies. The results of this meta-analysis determined that patients with chronic schizophrenia have decreased MMN amplitudes when compared to controls. This particular comparison is now considered 'established' due to the large effect size that describes the difference in mean amplitudes between controls and patients (Cohen's d = .99; Umbricht & Krljes, 2005). The attenuated amplitudes are reflective of auditory disturbances, which is considered an underlying pathophysiological mechanism associated with the onset of psychosis and schizophrenia (Bodatsch, Ruhrmann, Muller, Schultze-Lutter, Frommann, & Brochkaus-Durnke, 2011).

After generally accepting reduced MMN amplitudes in schizophrenia, studies examined how the domains of MMN (i.e. latency, duration, frequency) differed between patients with schizophrenia and healthy individuals. Michie, Budd, Todd, Rock, Wichmann, Box and Jablensky (2000) were among these researchers and examined the underpinnings of dMMN regarding the deficits in the auditory system of a patient with schizophrenia. However, their work

found significant reductions of MMN in schizophrenia for duration but not frequency deviants. These results supported the use of dMMN over other types of MMN in schizophrenic populations. Umbricht et al. (2003) results supported Michie et al. (2000) and also found that across studies, dMMN amplitudes were significantly reduced in patients with schizophrenia whereas frequency MMN did not reach significance. The meta-analysis by Umbricht and Krljes (2005) also provided further support for these findings, such that the calculations of effect sizes across studies revealed that dMMN effect size was twice as large as frequency MMN. The relationship between duration of illness and MMN amplitude was explored using a regression analysis where illness duration was separated based on the sample population's median (10.6 years) years since first hospitalization. The regression analysis showed a significant positive relationship between illness duration and dMMN amplitude effect size (ES), such that the longer duration had a 40% larger ES than shorter duration (Umbricht & Krjles, 2005).

Due to the substantial amount of clinical research that has found an effect using dMMN, other studies shifted and began to applied dMMN in hopes to relate this domain of MMN to duration of illness. Magno, Yeap, Thakore, Garavan, De Sanctis, and Foxe (2006) evaluated first-episode, chronic, and relatives of patients with schizophrenia and also found differences in dMMN amplitudes, but no effect in the pitch deviants. Todd, Michie, Schall, Karayanidis, Yabe, and Näätänen (2008) compared duration, frequency, and intensity deviants in early and late stages of schizophrenia. Again, findings revealed strong differences in dMMN, no significance in frequency deviants, and all significant effects increased with duration of the illness. Thus, dMMN has been referred to as one of the most robust and reliable evaluations of deficits in sensory information processing in schizophrenia (Light & Näätänen, 2013; Murphy et al., 2013; Umbricht & Krljes, 2005).

dMMN amplitudes have also been found to be significantly attenuated in both chronic and first-episode patients with schizophrenia. Salisbury, Shenton, Giggs, Bonner-Jackson, and McCarley (2002) found no difference in pitch MMN between first-hospitalization/first-episode patients with schizophrenia and healthy controls and concluded that MMN reductions may increase over duration of the illness. However, Salisbury, Kuroki, Kasai, Shenton, and McCarley (2007) completed a longitudinal study on first-episode patients which found that MMN reductions were significant 1.5 years after the first hospitalization. In Jahchan (2010)'s review of literature, the author describes three significant studies that confirmed differences in MMN amplitudes in patients with recent-onset/first-episode schizophrenia (Javitt, Shelley, Silipo, & Lieberman, 2000; Oades et al., 2006; Umbricht, Bates, Lieberman, Kane & Javitt, 2006). Jahshan, Cadenhead, Rissling, Kirihara, Braff, and Light (2012) investigated MMN across different stages of schizophrenia (at-risk, recent-onset, and chronic) and found the most significant reduction between recent-onset and healthy controls, but also a significant difference in amplitudes between at-risk and healthy controls.

There are a considerable number of disorders, other than schizophrenia, that also present sensory memory dysfunction. Therefore various domains of MMN have been applied to these disorders in anticipation of finding similar effects to those found in schizophrenia. These disorders include but are not limited to: dyslexia, autism, and language processing disorders. When comparing individuals with dyslexia to neurotypical controls, general trends have shown significant reductions in pitch and frequency MMN (Bartha-Doering et al., 2009). Bartha-Doering et al. (2015) also reported a reduced MMN in children with learning disabilities compared to typically developing children. MMN research examining autism spectrum disorders tends to have conflicting trends in different domains of MMN. Minimal studies have found

significant reductions using frequency deviants and at least one study found significant amplitude reductions using dMMN (Andersson, Posserud, & Lundervold, 2013; Dunn, Gomes & Gravel, 2007; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Fan & Cheng, 2014).

Present study

The significant difference reported in these studies between normal controls and clinical populations have led to reports suggesting that MMN should be considered as a useful tool to identify biomarkers in clinical populations (Nagai et al., 2013; Light & Näätänen, 2013). The MMN paradigm is thought to be reflective of the N-methyl-d-asparate receptor, pre-attentive auditory sensory memory, and the findings of attenuated MMN amplitudes are often found in patients with chronic schizophrenia (SZ) in literature. Therefore, Nagai et al. (2013) claimed these features provide support for MMN as a predictive tool to identify clinical stages of psychosis or furthermore, provide risk assessment information regarding the likelihood that an individual may develop psychosis.

In reference to psychosis, the prodromal stage is a critical developmental phase describing the early symptomatic periods of the illness. The prodromal stage is also characterized by gradual progression, which makes early identification difficult. Without proper identification, prevention and intervention techniques are challenging to establish. Therefore, the general consensus in literature is that prevention methods are the most effective approach to overcome psychosis; however, due to the fact that the origin and onset of psychosis is unclear, ERPs have demonstrated a reasonable measure to identify those who might be considered at risk for psychosis. In a meta-analysis, Bodatsch et al. (2015) examined MMN, among other ERP components, and discussed the clinical relevance of using dMMN as an informative tool for

prognosis of psychosis. Only 7 studies examined MMN in at-risk populations. The most robust effects were found using dMMN and at-risk and/or ultra-high-risk participants demonstrated significantly less negative amplitudes than the control group. The findings of this meta-analysis supported that future research should aim to evaluate the extent of MMN's specificity and sensitivity in order to ultimately transform this component into an early identification tool (Bodatsch et al., 2015).

The present study aimed to contribute to the development of MMN as an early detection tool by testing the extent to which MMN can distinguish between healthy and clinical populations. Thus, two types of deviants were used in the MMN paradigm with a relatively homogenous participant pool. The deviants differed from the standard in duration because dMMN maintains robust findings and is thought to be most representative of amplitude change as a function of illness duration (Umbrict & Krjles, 2005). The deviants were different from each other based on how closely they each resembled the standard tone, where one deviant was more elusive and the other was more obvious. This level of difficulty was used to assess if in comparison to their peers, the individuals placed in the prodromal group would demonstrate general temporal deficits or if there was one range of temporal dysfunction that could differentiate the two groups. The population did not contain a diagnosed clinical group. Instead, participants were grouped based on if they endorsed symptomology associated with psychosis. This was measured using the 16-item Prodromal Questionnaire (PQ). The expectation was if MMN was successful at distinguishing between these populations that likely differ to a much smaller degree than controls compared to individuals with a diagnosed condition (i.e. psychosis or schizophrenia), then this would further support the development of MMN as an early detection tool.

The first analysis aimed to compare a high-risk group to a clean control group to see if MMN could distinguish the extreme ends of this nonclinical population. The second analysis aimed to replicate trends seen in literature that compares patient with chronic schizophrenia to healthy controls by using the established cut-off score of 6 to group participants. The third analysis took an exploratory approach and applied regression analyses to examine if the magnitude of MMN amplitudes would decrease as a function of increased symptomology as shown by higher PQ scores. The hypothesis of the present study was that participants who met the criteria for high-risk for psychosis based on the PQ would have attenuated dMMN amplitudes compared to the control group.

METHODS

Participants

A survey screening for high-risk for psychosis (16-item Prodromal Questionnaire, *DSM-IV*) was administered to undergraduate, introductory level psychology students at a large university as part of a larger screening survey that also included demographic information. Power analysis revealed that in order to have 80% power each group would need to have 12 participants.

Participants were recruited and assigned to participant groups based on their survey scores from the 16-item Prodromal Questionnaire (PQ). The traditional, established cut off score of the PQ is 6. Controls are determined if a participant scored below a 6 on the PQ and those who score a 6 of higher are may be at risk of developing psychosis. Therefore, these participants who scored greater than or equal to a 6 on the PQ were placed in the high-risk (HR) group for purposes of Analyses 1 and 2. Controls selected differently for Analysis 1, which aimed to achieve a 'clean' control group. This was determined using the following criteria: 1) Received a total survey score of 0 on the Prodromal Questionnaire (PQ). 2) Did not report any previous diagnoses of a neurological or psychiatric disorder. 3) Did not report substance abuse. 4) Did not report diagnosis of a neurological or psychiatric disorder or substance abuse in immediate family. 5) Matched a high-risk participant based on age, sex, and ethnicity. Controls were selected using this strict criterion due to the comorbid and confounding variables outlined in Psychiatric Research Institute (2014), which included: substance use, low IQ, severe OCD, and other factors.

The survey alone is not considered a diagnostic tool; therefore, participants who scored over the 6 point cut-off score are not considered at risk, but based solely on self-reported symptoms qualified for the high-risk (HR) group for purposes of this study. This study met the criteria for IRB approval. All participants signed consent forms and were provided with contact information after the study. Participation was voluntary and anonymous and participants were treated in accordance with the "Ethical Principles of Psychologists and Code of Conduct" (American Psychological Association, 2010). Participants debriefing forms with appropriate contact information and supplementary information regarding the study. Participants received extra credit for participation.

Materials

16-Item Prodromal Questionnaire: The Prodromal Questionnaire (PQ) has been used as screening stage 1 of 2 for psychosis. Ising et al. (2012) determined the reliability of the 16-item questionnaire using a ROC analysis: 87% sensitivity, 87% specificity, 44% positive predictive values. Internal consistency reached an alpha level of .77 and achieved congruent validity with the Comprehensive Assessment of At-Risk Mental State (CAARMS; Yung et al., 2005) diagnosis ($r = .572$, $p < .01$; Ising et al., 2012). The 16-item PQ has highly comparable reliability and validity scores compared to the original 92-item PQ and, therefore, is considered to meet the criteria for use as a screening instrument (Ising et al., 2012).

The 16-item PQ responses were coded as 0's for "*false*" and 1's for "*true.*" If participants answered "*true*," the questionnaire asks for level of severity. The possible responses for level of severity are "*mild*," "*moderate*," or "*severe*" and were coded as 1, 2, or 3 respectively. The appropriate methods for scoring according to Ising et al. (2012) does not include the numerical

values associated with "*mild*," "*moderate*," and "*severe*" in the final score. The highest possible score on the 16-item PQ was 16 points and the lowest possible score was 0 points. The generally accepted cut-off score is 6 (Ising et al., 2012). Therefore, all participants who score a 6 or higher were placed in the high-risk group.

Procedure

MMN Paradigm: Brainwaves were recorded using an EEG (NeuroScan 4.0 system). Electrode placements followed the 10-20 system and included the following locations: *Fz, Cz, Pz*, left and right mastoids, lateral and superior of the right eye, a ground electrode from the forehead, and a reference electrode from the tip of the nose. Participants were presented with 2880 samples (120 cycles of 24 samples) of randomized tones (Standard = 500 ms; Deviant 1 = 425 ms; Deviant 2 = 250 ms) through headphones. The standard interval was 500 ms and there were deviant intervals of both 450 ms and 250 ms between tones for a total time of approximately 30 minutes. The Deviant 1 tone and Deviant 2 tone were programmed to each occur 4 % of the time and the standard tone was presented 92% of the time.

Data analysis: The recorded signals were separated into epochs (400 ms) with a 100ms pre-stimulus interval relative to time pulses. For baseline correction, the average voltage of the 100 ms pre-stimulus interval was subtracted from each signal trial (tone-onset: time = 0). Artifact rejection was set to +/- 250 Hz and all trials where a channel's voltage exceeds +/- 75 µV were removed. For each participant, standard and deviant evoked responses were averaged then the standard averages were subtracted from the deviant averages to determine the MMN amplitude. The MMN amplitude was the peak negative amplitude occurring between 140 and 210 ms after

the onset of the deviant tone. Any positive MMN amplitudes remaining were removed. Based on this criteria, all participants who were missing data from 1 electrode or more were removed entirely from analysis.

RESULTS

Three analyses were applied to the dataset in order to compare the traditional method of grouping against a different method of grouping and to compare an alternative method of analysis all together. According to Ising et al. (2012), the established cut off score for the 16-item PQ is 6. Thus the second analysis used this conventional method to analyze the data. The first analysis however, attempted to examine the clean control group and the third analysis aimed demonstrate a linear relationship between the survey and MMN amplitudes

Analysis 1

The first analysis identified 13 individuals who met criteria for the clean control group and 63 individuals who met criteria for inclusion in the HR group according to the traditional cut-off score. A *t*-test was used to evaluate mean difference between Group 1 (Control) (n = 13) and Group 2 (HR) (n = 54) at each electrode location (*Fz, Cz,* and *Pz*) (see Table 1). For Deviant 1 at the *Cz* electrode, Group 1 (Control) had a mean amplitude of -2.39 (*SD* = 1.56) and Group 2 (HR) had a mean of -2.10 (*SD* = 1.26). For Deviant 1 at *Fz,* Group 1 Controls had a mean amplitude of -1.60 (*SD* = 1.17) and Group 2 (HR) had a mean of -1.70 (*SD* = 1.06). For Deviant 1 at *Pz,* Group 1 (Control) had a mean amplitude of -1.77 (*SD* = 1.40) and Group 2 (HR) had a mean of -2.05 (*SD* = 1.27).

For Deviant 2 at the *Cz* electrode, Group 1 (Control) had a mean amplitude of -5.60 (*SD* = 3.34) and Group 2 (HR) had a mean of -5.03 (*SD* = 2.74). At *Fz,* Group 1 Controls had a mean amplitude of -3.68 (*SD* = 2.03) and Group 2 (HR) had a mean of -3.71 (*SD* = 2.15). For *Pz,* Group 1 (Control) had a mean amplitude of -3.09 (*SD* = 2.55) and Group 2 (HR) had a mean of -

2.55 (*SD* = 1.94). Each electrode location was examined using a *t*-test to compare the clean control group to the HR group. Deviant 1 demonstrated no significant differences at any of the electrode locations (*Cz: t*(65) = -.702, *p* = .485; *Fz*: *t*(65) = .311, *p* = .757; *Pz*: *t*(65) = .712, *p* = .479). Deviant 2 also demonstrated no significant differences at any of the electrode locations (*Cz: t*(65) = -.646, *p* = .521; *Fz*: *t*(65) = .043, *p* = .966; *Pz*: *t*(65) = -.837, *p* = .491) (see Figure 3).

Analysis 2

The second analysis used the traditional cut-off score of 6 to compare statistical results, such that participants who scored below a 6 on the PQ were placed in the control group (*n* = 63) and participants who scored a 6 or higher were placed in the HR group (*n* = 54). Findings demonstrated a significant trend such that *Fz* and *Cz* electrodes were significant for Deviant 2 (*Cz: t*(115) = -2.11, *p* = .02; *Fz*: *t*(115) = -2.26, *p* = .01; *Pz*: *t*(1) = -1.30, *p* = .10) (see Table 2). None of the electrodes reached significance for Deviant 1; however, the *Cz* electrode did approach significance (*Cz: t*(115) = -1.44, *p* = .077; *Fz*: *t*(115) = -.42, *p* = .338; *Pz*: *t*(1) = .38, *p* = .352) (see Figure 4).

Analysis 3

The third analysis took a different approach and aimed to linearly describe the relationship between symptomology and MMN amplitudes through a regression analysis. The grand means for each electrode location for all 117 participants used in the regression analysis were as follows: For Deviant 1, *Cz* mean amplitude was -2.28 (*SD* = 1.23), *Fz* mean amplitude was -1.75 (*SD* = 1.03), and *Pz* mean amplitude was -2.01 (*SD* = .35). For Deviant 2, *Cz* mean

amplitude was -5.57 (*SD* = 2.61), *Fz* mean amplitude was -4.15 (*SD* = 1.98), and *Pz* mean amplitude was -2.79 (*SD* = 1.84). The average score on the survey was 5.81 (*SD* = 4.70) and all survey scores were represented by at least three participants. Deviant 2 demonstrated a significant linear relationship at *Fz* (R^2 = .034, p = .047) and the *Cz* (R^2 = .027, p = .077) electrode approached significance (see Table 3 & Figure 5). Again, Deviant 1 did not demonstrate any significant relationships.

DISCUSSION

The purpose of the present study was to evaluate the extent to which MMN could distinguish between groups of a relatively homogenous population. Therefore, the relationship between MMN amplitudes and the 16-item Prodromal Questionnaire's established cut-off scores was examined using 2 deviants that varied by in degree of distinction from the standard deviant in a nonclinical population. The participants, although not clinically diagnosed, completed a survey used in clinical screenings for psychosis prognosis and separated into groups based on survey scores. The hypothesis was that controls would demonstrate larger negatively deflected amplitudes on average than participants considered at high-risk for psychosis. Furthermore, the study sought to compare three analyses to better demonstrate the continuum nature of disorders, address possible issues with using a cut-off score, and provide support for MMN's development into a predictive tool for the onset of psychosis.

Trends of reduced MMN amplitudes and shorter latencies have been found in literature when the extent to which a deviant differs from a standard tone is manipulated (Horton, Millar, Labelle, & Knott, 2011). However in the present study, Deviant 1 did not demonstrate any significant relationships in any of the three analyses or electrode locations. Deviant 2 represented a more discernable auditory element than Deviant 1. Due to the more subtle nature of Deviant 1, differences in amplitudes were expected to be small if at all existent. The intended use of both types of deviants was to see if creating more subtle deviants could better define and increase MMN's application as a detection tool between those who self-report symptoms of psychosis and those who do not. Since the individuals who demonstrated less symptomology were not statistically better at detecting subtle differences than large differences in deviant tones, these

results suggested that degree of deviance might play a critical role in terms of the utility of the use of MMN as a detection tool for psychosis.

The following inferences of findings refer to the results of Deviant 2 only. Two *t*-tests were used to compare traditional methods of analysis and an exploratory analysis. Analysis 1 screened for a 'completely' clean control group, meaning the participants had to score a 0 on the prodromal survey and not report diagnoses, family history of diagnoses, and substance use by self or immediate family. Analysis 2 used the traditional style of grouping based on the established 6 point cut-off score. Findings suggested that the clean control group did not have a more negative MMN; however, when participants were grouped based on the cut-off score, results followed the trend in literature and became statistically significant (Umbricht & Krjles, 2005).

Therefore, another exploratory analysis was applied to the dataset. Analysis 3 used simple linear regressions at each electrode location to demonstrate a linear effect of prodromal scores and attenuated MMN amplitudes. Simple linear regressions related MMN amplitudes to survey score at each electrode location. As expected, multiple linear regressions results demonstrated a nonsignificant relationship. This was due to the violation of assumptions and high correlation amongst electrodes and, therefore, was not reported. Furthermore, the procedural design of this experiment did not intend to localize, thus, the minimum number of electrodes required for recording were placed on the temporal-frontal cortical network. The results of the exploratory regression analysis demonstrated similar findings to the traditional grouping method. The same electrode locations that demonstrated a significant effect in Analysis 2 (Traditional) were significant or approaching significance in Analysis 3 (Regression) - further supporting the use of regression analysis for research on diagnosis criteria.

Simple linear regression analyses may offer a more appropriate model to relate self-reports of symptomology and MMN amplitudes. Pedhazur (1997) offers support for using regression to relate a diagnostic survey and electrophysiological tool in referencing that practical applications of regression in behavioral sciences include prediction, classification, and explanation. Therefore, as MMN research moves towards developing MMN as a prediction tool, regression may be a more suitable analysis. Current shifts in stigma and diagnostic criteria have begun to view disorders as spectrums or continuums, which have resulted in regression analyses to inform classification and predispositions for disorders (Davidson, Reichenberg, Rabinowitz, Weiser, Kaplan, & Mark, 1999; Greenstein et al., 2014). The standard methods of diagnostic grouping should be reevaluated in terms of this alternative view.

Davidson et al. (1999) were among early researchers who built a regression model aimed to improve the accuracy of predicting those who were predisposed for schizophrenia. This model incorporated behavioral, cognitive, and demographic data, and interviews and successfully classified patients and non-patients back into the appropriate groups. Other previous literature has used regression analysis to examine characteristics that are or are not specific to clinical groups. Tien, Ross, Pearlson, and Strauss (1996) analyzed oculomotor performance, symptom surveys, and cognitive tasks to evaluate how performances on specific tasks were related to bipolar and schizophrenic patient groups. Thus, the information that can be gained from use of linear analysis over grouping constructs may be more informative and better representative of the relationship between psychosis and MMN amplitudes. Using a regression analysis over a cut-off score is one way to demonstrate disorders on a continuum from a research perspective.

The importance of a stronger, more accurate diagnostic evaluation method stems from the necessity to improve prevention strategies for individuals at-risk for psychosis. Currently, if an

individual is identified as at-risk for developing psychosis, there is no method of action for this individual to partake to increase prevention of onset. Typically, the prognosis includes lowering stress levels and refraining from drug use. Since these items (stress, drugs) are associated with the onset of psychosis, individuals in undergraduate facilities are likely exposed to a greater number of risk factors associated with development of psychosis, especially if they meet the criteria for predisposition to schizophrenia. The present study consisted of undergraduate students who presented self-reports of symptomology associated with psychosis. Participant's timing or temporal perception was evaluated based on MMN amplitudes, which reflected short intervals. Since long intervals were not included in the present study, no conclusions were drawn regarding the role of working memory and/or attention on the ERP paradigm.

Limitations and Future Research

Although an effect was found, there were limitations to the present study. There was limited diversity across the participant pool and samples were drawn from an undergraduate psychology course. The psychometric properties of the questionnaire supports its application as an identification instrument for those who may be at-risk for psychosis but does not offer enough empirical basis for a true diagnosis of a current psychotic disorder. However since an effect was found, findings further supported dMMN as a viable option for detecting subtle differences in a population that would be perceived as healthy and future research will aim to follow participants to identify those who convert into psychosis or schizophrenia to strengthen the predictive qualities of dMMN.

All participants were grouped based on self-report. Thus, indicating of prior diagnoses of self or immediate family was up to the discretion of the participants and may result in either

intentional or accidental deceit. Participant may not be aware of all family diagnoses or wish not to report family or self-diagnoses due to confidentiality. Alternatively, participants may indicate a diagnosis based on speculation as opposed to a true, clinical diagnosis. This limitation could have skewed the control group and resulted in misidentification of participants.

There was a large difference in number of participants who fit the criteria for 'clean' control. Although the sample size of the 'clean' controls was large enough to retain power, the sample size of the at-risk group was approximately five times as large. The variation in sample size across groups may offer an explanation for why results did not retain significance. In order to address this issue, either data must continue to be collected or the criteria for the 'clean' control group should be readdressed.

A portion of the criteria for the 'clean' control group required participants to score no more than a 0 on the PQ. However, there was no reverse coding for this standardized survey and therefore, those who scored a 0 might lead to inaccuracies in the data. This was most likely an issue in the present study and can be seen in the high variability of the amplitudes in participants who scored a 0, specifically in Analysis 1 'clean' control group (survey scores = 0).

In order to fully account for the difference of survey scores and variation between groups, data will continue to be collected. This way the present study will attribute more power to each survey score and a stepwise analysis comparing amplitudes at each level or each score can be completed. This analysis stage will hopefully provide support for MMN's distinguishing ability in potentially clinical populations.

The present study did not attempt to address localization of MMN in subclinical populations. Addressing potential neural correlates is outside the scope of this project; however, any regions that would mediate deficits in the subclinical population would correspond to

regions that are associated with early temporal processing. Based on literature and theoretical implications, these regions would include those associated with MMN: temporal regions, specifically the superior temporal gyrus and the inferior frontal gyrus in frontal areas. Since this paradigm did not include a task that would elicit structures involved in memory and attention, these regions would not have been of concern.

Since subclinical populations typically present deficits with the cognitive processes that underlie timing theory, the present study attempted to isolate timing deficits through use of MMN. In relation to psychosis, patients with chronic SZ demonstrate a multitude of issues when completing tasks involving working memory or sustained attention. The population of the present study consisted of participants who scored high on a survey used to screen for at-risk of psychosis. Since this type of psychosis relates to the prodromal stages of schizophrenia, our participants may have had similar shortfalls in working memory or attention. Therefore, the paradigm used in this research made these cognitive processes irrelevant and truly isolated the nature of the timing deficits in this population. However, localization information may have been useful in conjunction with isolated timing effects: If the participants who demonstrate similar deficits in memory and attention to patients with chronic SZ are the same participants as those who have attenuated MMN amplitudes compared to controls, then this may provide more information about pinpointing who will convert from normally functioning to prodromal stages. Thus, future research will include information about localization to further develop the predictive value and clinical relevance of MMN.

As previously stated schizophrenia presents large deficits in timing capabilities and therefore individuals who meet criteria for psychosis may also demonstrate these deficits. Without an ability to process time in a linear fashion, individuals would not be able to carry out

day to day functions required in today's society including: responding to events, sequencing events, executive functions, such as planning and decision-making. This would prove to be particularly detrimental for undergraduate students. The cognitive processes that underlie timing are also necessary for success in an academic environment. By using MMN to isolate timing function from these cognitive influences, researchers can aim to localize where deficits in timing originate. However, an analysis of long intervals (seconds to minutes range) was not included in this research and therefore no information regarding memory and attention function can be assessed.

Future research will also include examination of longer time intervals in this subclinical population in order to generalize findings to an academic setting. The present study remained within a very short time interval (millisecond range) and therefore, the memory and attention function was not assessed. Since the population was derived from an academic setting, examining temporal perception at short and long intervals could provide more information regarding pathology. If healthy students are demonstrating deficits in longer intervals, then deficits may be more related to attention and memory function. However, if deficits can be pinpointed to early information processing stages as demonstrated by MMN, then decreased academic performance due to abnormalities of time perception may be more related to pathology (Rubia, 2006).

Current research has examined MMN across multiple clinical disorders and especially with disorders associated with auditory disturbances (i.e. dyslexia). Although the current project examined a subclinical population, future research will aim to evaluate early symptomatology associated with other disorders that present deficits in early information processing. Future research will also aim to examine MMN and symptoms associated with psychosis, delusional

disorder, and schizotypal personality disorder. Furthermore, MMN's application may not be limited to diagnosis. Based on literature, behavioral training has been examined in clinical and healthy populations to examine if a physiological change, marked by more negative MMN amplitudes, can be elicited post-training. This supports MMN's therapeutic application and future research will attempt to further explore this claim.

Summary

Although, differentiating between a strictly healthy control group and a group that demonstrated symptomology associated with prodromal stages of psychosis is useful, this was a foundation for future development of MMN. Based on the findings of this study, MMN could be a useful tool as a part of a larger battery to better inform diagnosis.

Due to the gradual nature of psychosis, early recognition is difficult but also thought to be the most reliable opportunity to defer the development of psychosis. Therefore, Nagai et al. (2013) argued for the MMN paradigm as a translatable clinical biomarker to identify early signs of psychosis. Present results supported Nagai et al. (2013) and the use of dMMN as an informative, predictive measure to identify individuals who are currently prodromal or may develop psychosis. This practical application may also be informative about the underlying pathology of prodromal stages of psychosis.

Results suggested that MMN was not successful in discriminating those who classify as clean controls and those who score above the 6 point cut-off score. The survey alone does not suffice a diagnosis and significant findings guide the direction research should take to further develop MMN's ability to distinguish between clinical groups. An additional analysis also demonstrated a significant linear relationship between scores and MMN amplitude at *Fz*. Results

may provide a useful tool for identifying those students who are generally thought to be high-functioning, but may be at-risk for later development of psychosis or cognitive and psychological difficulties associated with psychosis.

Table 1

Statistics for Analysis 1 t-tests

Descriptives		Deviant 1			Deviant 2		
		Cz	*Fz*	*Pz*	*Cz*	*Fz*	*Pz*
Control							
n	13						
$\bar{x}$		-2.39	-1.60	-1.77	-5.60	-3.68	-3.09
SD		1.56	1.17	1.40	3.34	2.03	2.55
Prodromal							
n	54						
$\bar{x}$		-2.10	-1.70	-2.05	-5.03	-3.71	-2.55
SD		1.26	1.06	1.27	2.74	2.15	1.94
t-statistic		-.702	.311	.712	-.646	.043	-.837
p-value		.485	.757	.479	.521	.966	.491

Note: All comparions are made between ‘clean’ control group and symptomatic for at-risk at each electrode location.

Table 2

Statistics for Analysis 2 t-tests with Traditional Cutt-Off Score

Descriptives		Deviant 1			Deviant 2		
		Cz	*Fz*	*Pz*	*Cz*	*Fz*	*Pz*
Control							
n	63						
$\bar{x}$		-2.42	-1.78	-1.96	-6.04	-4.52	-2.99
SD		1.18	1.02	1.55	2.24	1.76	1.75
Prodromal							
n	54						
$\bar{x}$		-2.10	-1.70	-2.05	-5.03	-3.71	-2.55
SD		1.59	1.12	1.27	2.74	2.15	1.94
t-statistic		-1.48	-.42	.38	-2.11	-2.25	-1.30
p-value		.076	.33	.35	.018*	.013*	.098

Note: All comparions are made between control group (<6) and symptomatic for at-risk (>6) at each electrode location.

Table 3

Statistics for Analysis 3 Simple Linear Regression

Descriptives	Deviant 1			Deviant 2		
	Cz	*Fz*	*Pz*	*Cz*	*Fz*	*Pz*
N 117						
$\bar{x}$	-2.30	-1.76	-2.04	-5.64	-4.20	-2.86
SD	1.22	1.03	1.25	2.58	1.94	1.73
R^2-statistic	.016	.001	.002	.02	.03	.02
p-value	.173	.656	.858	.07	.04*	.132

Note: Grand mean and standard deviations for all simple linear regressions.

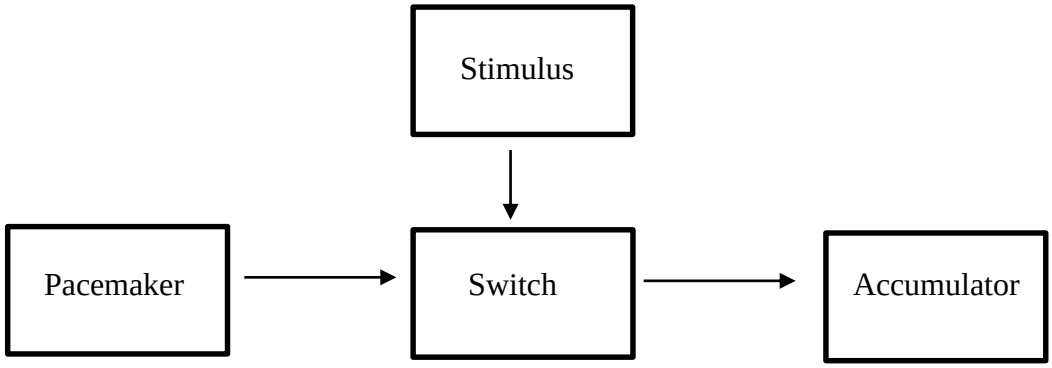

Figure 1. Internal Clock Hypothesis Diagram. When a stimulus is present, the accuracy of the switch is influenced and therefore the number of STUs counted in the accumulator is also effected. Adopted from Grondin (2010).

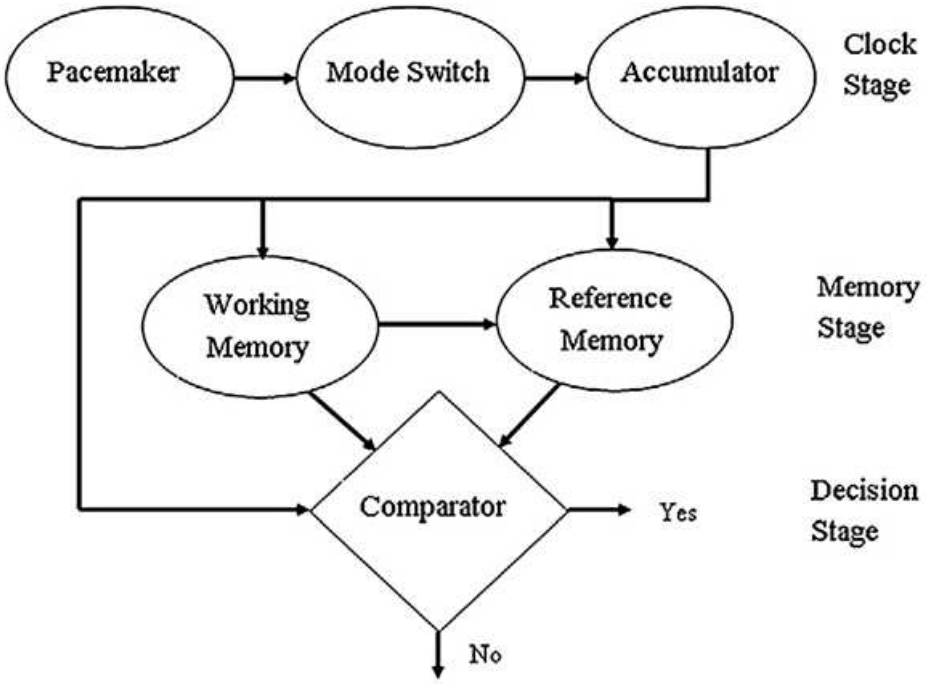

Figure 2. A Comprehensive Design of the Stages of the Scalar Expectancy Model. Adopted from Grondin (2010).

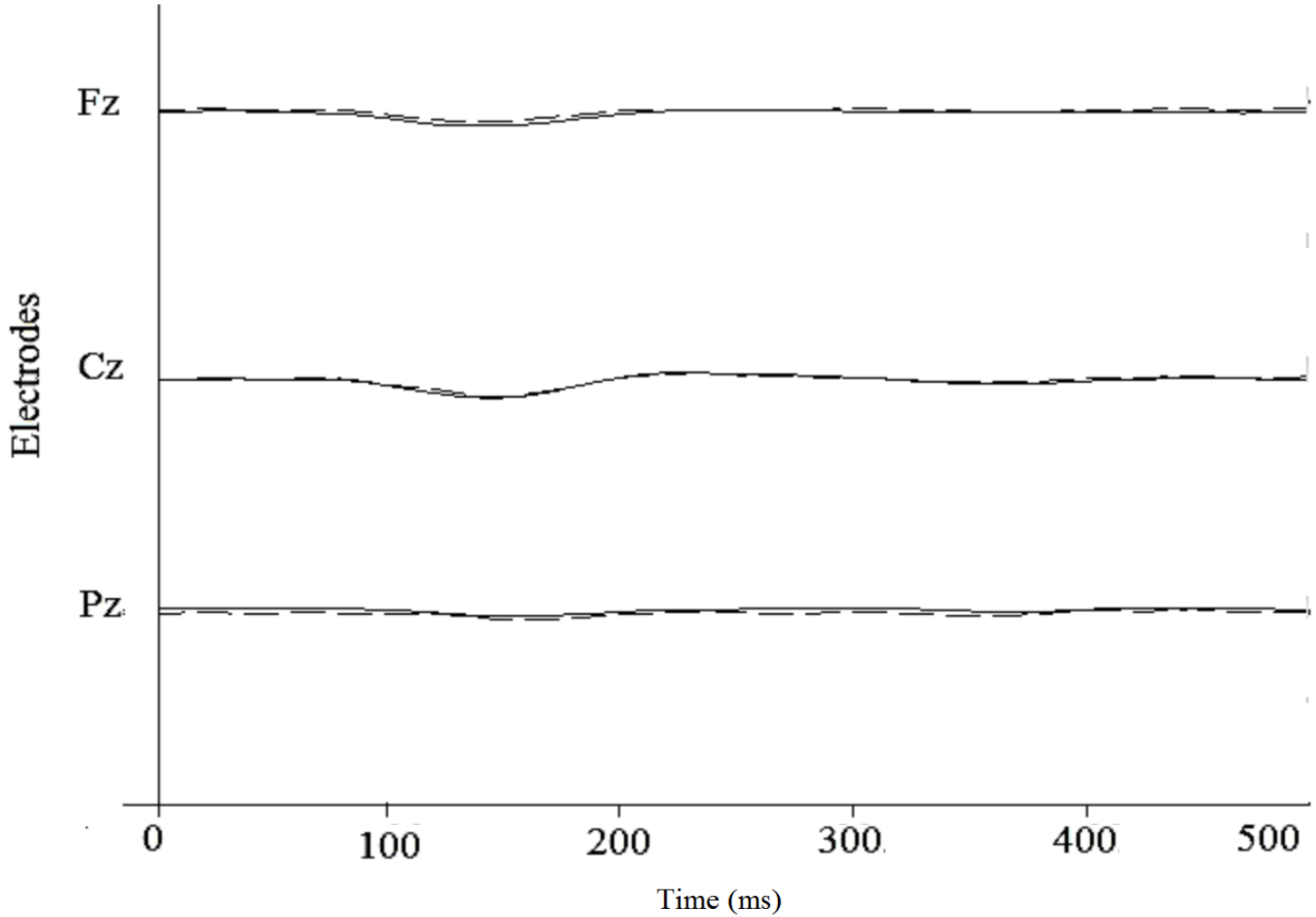

Figure 3. Analysis 1 Group Comparisons of Deviant 2 MMN Amplitudes
Note. Control group waveforms are indicated in black. Dotted lines represent the PRO (Score = 0) group waveforms.

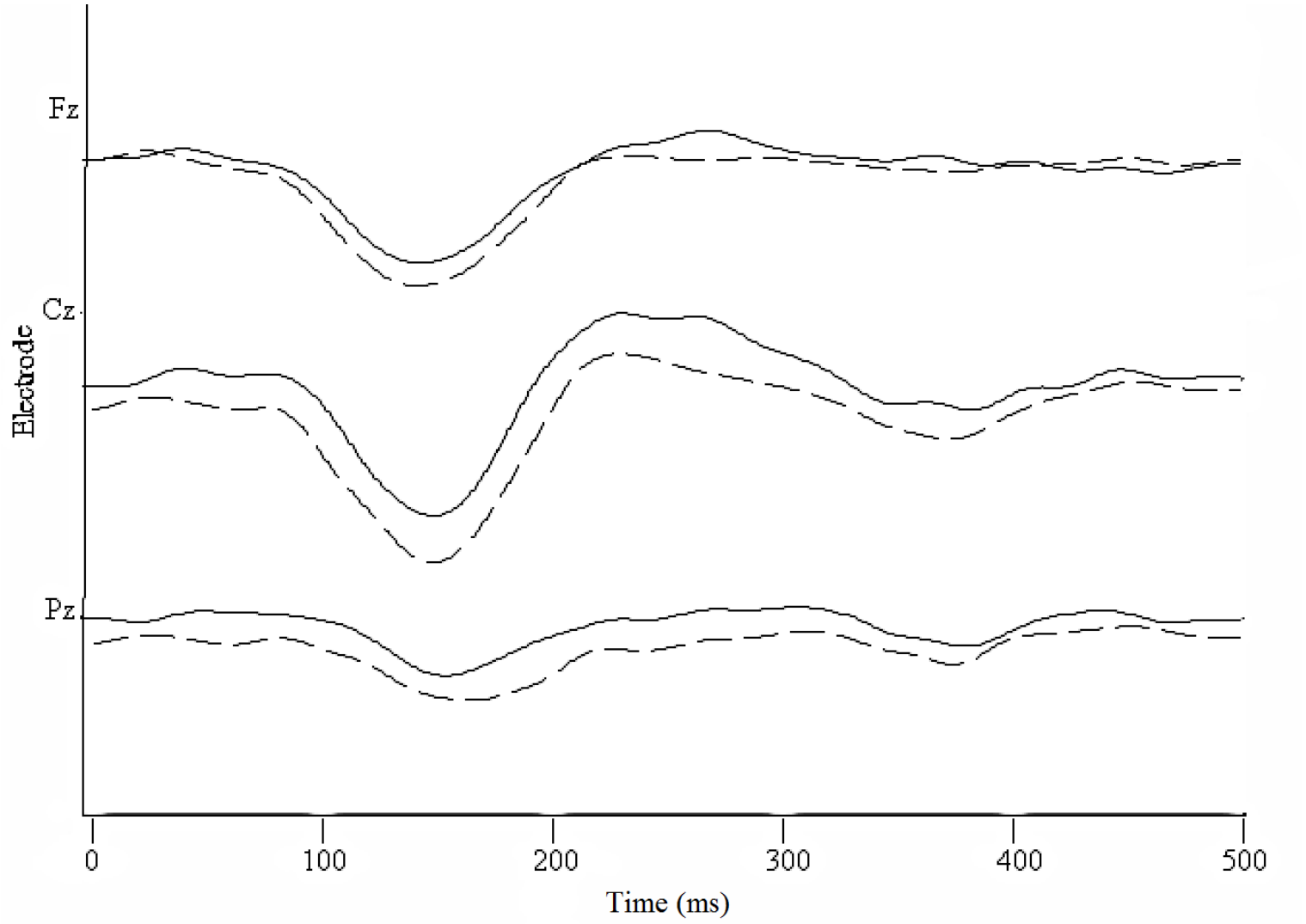

Figure 4. Analysis 2 Group Comparisons of Deviant 2 MMN Amplitudes at Each Electrode Location
Note. Control group waveforms are indicated in black. Dotted lines indicate PRO (Score < 6) group waveforms.

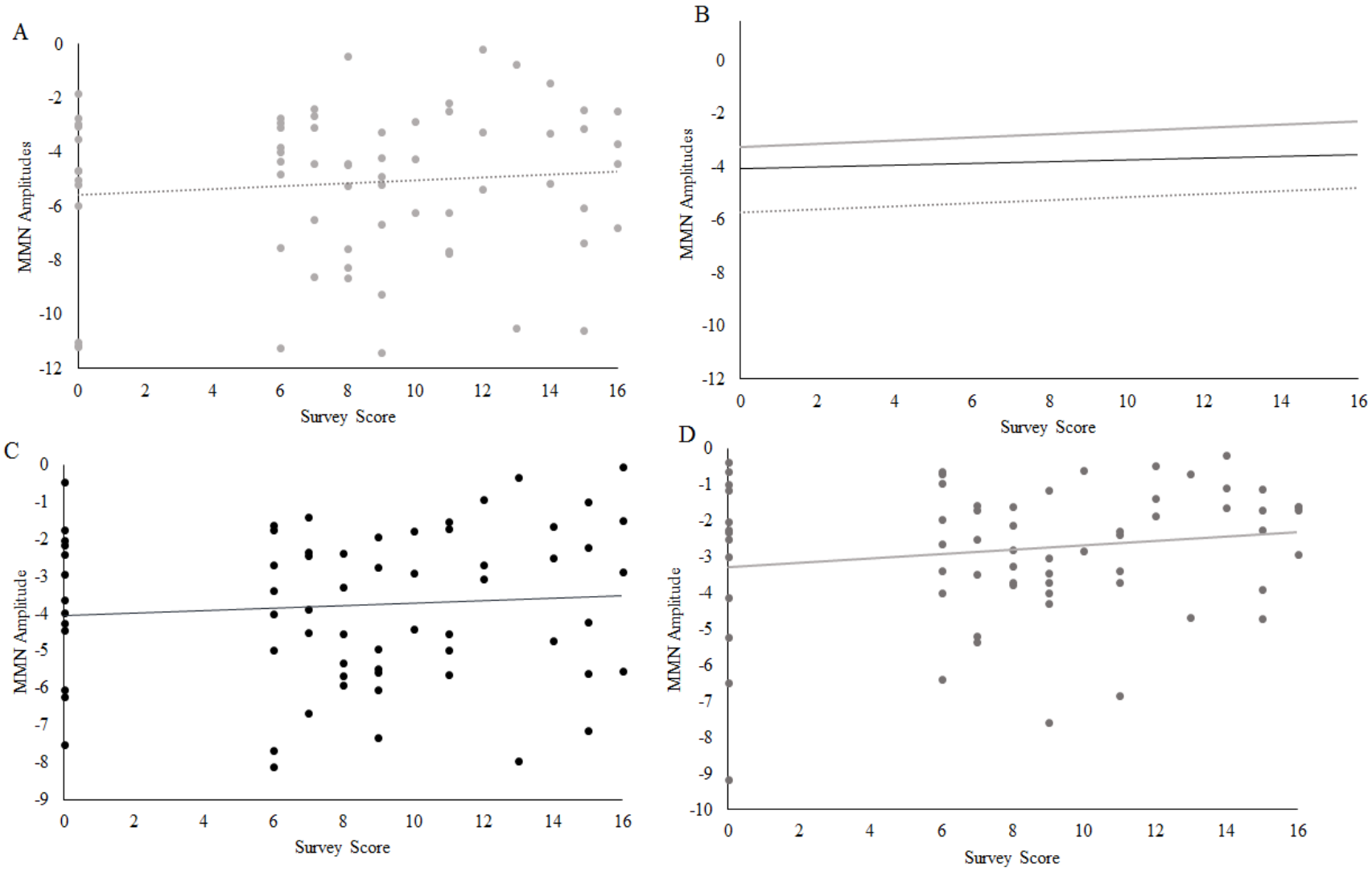

Figure 5. Analysis 3 Scatterplots by Electrode Location and Trend Lines
Note. Graph A is *Fz*, Graph B trend lines of *Pz*, *Fz*, and *Cz* from top to bottom. Graph C is *Fz* and Graph D is *Pz*.

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