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Finding the missing-stimulus mismatch negativity (MMN) in early psychosis: Altered MMN to violations of an auditory gestalt

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Abstract

The mismatch negativity (MMN) is an EEG-derived event-related potential (ERP) elicited by any violation of a predicted auditory ‘rule’, regardless of whether one is attending to the stimuli, and is thought to reflect updating of the stimulus context. Chronic schizophrenia patients exhibit robust MMN deficits, while MMN reduction in first-episode and early phase psychosis is significantly less consistent. Traditional two-tone “oddball” MMN measures of sensory information processing may be considered too simple for use in early phase psychosis in which pathology has not progressed fully, and a paradigm that probes higher order processes may be more appropriate for elucidating auditory change detection deficits. This study investigated whether MMN deficits could be detected in early phase psychosis (EP) patients using an abstract ‘missing stimulus’ pattern paradigm (Salisbury, 2012). The stimuli were 400 groups of six tones (1000 Hz, 50 ms duration, 330 ms stimulus onset asynchrony), which was presented with an inter-trial interval of 750 ms. Occasionally a group contained a deviant, meaning that it was missing either the 4th or 6th tone (50 trials each). EEG recordings of 13 EP patients (5 year duration of illness) and 15 healthy controls (HC) were collected. Patients and controls did not significantly differ on age or years of education.

Analyses of MMN amplitudes elicited by missing stimuli revealed amplitude reductions in EP patients, suggesting that these deficits are present very early in the progression of the illness. While there were no correlations between MMN measures and measures such as duration of

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Contributors

Author ER recruited control participants, collected electrophysiological data, managed the literature searches and analyses, undertook the statistical analysis, and wrote the first draft of the manuscript. Author DF designed the study and wrote the protocol. Author PT recruited and assessed patient participants and edited the final manuscript. Authors EE, DC and SA recruited control participants and collected electrophysiological data. Author DS contributed to study design and data interpretation and edited the final manuscript. All authors have approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

illness, medication dosage or age, MMN amplitude reductions were correlated with positive symptomatology (i.e. auditory hallucinations).

These findings suggest that MMNs elicited by the 'missing stimulus' paradigm are impaired in psychosis patients early in the progression of illness and that previously reported MMN-indexed deficits related to auditory hallucinations in chronic patients may also be present in EP patients. As such, this paradigm may have promise in identifying early processing deficits in this population.

Keywords

MMN; Mismatch negativity; Schizophrenia; Auditory hallucinations; Auditory event-related potentials; Early psychosis

1. Introduction

Schizophrenia is one of the most severe and devastating brain diseases, affecting more than 1% of the world's population (American Psychiatric Association, 2013). Despite years of research, the underlying pathophysiology is still largely misunderstood. The characteristics of schizophrenia include alterations in cognition and behavior, which can make it quite difficult for individuals to carry out their normal routines.

Early phase psychosis (EP) is the critical phase within five years of an individual's first psychotic break (Larsen et al., 2010). Schizophrenia is associated with progressive social and functional decline during the early course of the disease, and peri-onset progressive pathology and pathophysiology have been demonstrated (Hirayasu et al., 1998; Kasai et al., 2003; Salisbury et al., 2007). There is a need for sensitive diagnostic tools that will facilitate the identification of psychosis as early diagnosis and phase appropriate treatments will lead to better outcomes (Insel, 2010). Early intervention services for psychosis would benefit from biomarkers of illness; one field of research that may aid in the identification of biomarkers for early phase psychosis is that of event related potentials (ERPs).

The cognitive and perceptual processing in the brain in schizophrenia can be assessed using a non-invasive measure of neuroelectric brain activity at the scalp, the electroencephalogram (EEG). When an individual processes a specific internal or external stimulus, such as a sound, the EEG shows the systematic changes that take place during that time (Näätänen, 2003). One of those types of changes involves event-related potentials (ERPs); a series of scalp-positive and scalp-negative voltage deflections that are locked to a particular stimulus event by time and phase. Following multiple stimulus repetitions, ERPs can be easily extracted from the EEG by time domain analysis and averaging EEG activity (Kappenman and Luck, 2012). ERPs are regularly used in psychological research because they can provide valuable insights into basic cognitive mechanisms as well as higher brain functioning well before the performance of an overt response (van der Stelt and Belger, 2007). Not only can ERPs help disentangle stimulus evaluation from response selection and execution processes, but certain ERPs are indices of automatic sensory perception that do

not require any behavioral response from an individual and may not require the individual's attention to the stimuli at all (Näätänen, 2003).

One of the most robust neurophysiological deficits of schizophrenia is auditory change detection, the ability to automatically and pre-attentively detect a change in the auditory environment. It is indexed by the EEG-derived mismatch negativity (MMN), a neurophysiological signal of auditory processing provided by the ERPs (Näätänen et al., 2007). MMN is thought to reflect detection of change from stimulus constancies in the environment (Salisbury, 2012). It is commonly generated by randomly inserting rare deviant auditory stimuli into a train of standard sounds. To elicit MMN, the deviant can be different from the standard in any number of ways, including deviations in frequency, duration, intensity, and location (Näätänen and Alho, 1997). The older memory trace model of MMN posits that before detecting auditory change, the central auditory system first forms a sensory memory representation of the standard grouping of sounds, and then uses this representation to compare against other incoming sounds. The MMN is generated when an incoming deviant does not match the representation, sending a signal to the executive mechanisms and interrupting the current cognitive processes in order to shift attention towards the deviant sounds (Näätänen et al., 2007). A newer prediction error model suggests that the auditory cortex derives a pattern of the auditory environment and that deviations from the complex pattern elicit an error signal from primary to secondary cortices used to adjust the model (Winkler, 2007). The error prediction model better explains how MMN can be elicited by violations of an abstract rule, which may relate only to the relationship between sounds, and how, in certain cases, MMN may be elicited by a repeated tone.

Individuals with chronic schizophrenia display deficits in basic sensory information processing, as reflected in the consistent reports of deficits in MMN amplitudes (as reviewed in Näätänen and Kahkonen, 2009). Although psychosis can also be found in other disorders, such as bipolar disorder (Salisbury et al., 2007), MMN deficits have been found to be unique to schizophrenia (Umbricht et al., 2003; Salisbury et al., 2007; Baldeweg and Hirsch, 2015). Whether the simple two-tone MMN is reduced in first episode schizophrenia is controversial. Several groups have reported normal MMN at first break (Salisbury et al., 2002, 2007; Umbricht et al., 2006; Magno et al., 2008). Other studies have reported that MMN deficits appear to be present at the first psychotic episode, and sometimes even before an individual's psychotic break (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2011; Atkinson et al., 2012; Kaur et al., 2013). However, previous findings have been very inconsistent and have only focused on traditional MMN. For example, Bruggemann et al. (2013) found increased MMN in ultra-high risk children. Traditional two-tone MMN measures of sensory information processing may be considered too simple for use in early phase psychosis in which pathology has not progressed fully, and a paradigm that probes higher order processes may be more appropriate for elucidating auditory change detection deficits.

One such complex pattern MMN paradigm was recently developed by Salisbury (2012). Based on the Gestalt principle of grouping by proximity, the paradigm is unique because its mismatch is the absence of a sound rather than the presentation of a new one. Using only one repeated tone, 330 ms apart, in groups of 6 separated by a 750 ms inter-trial interval,

MMN was elicited by a missing last 4th or 6th tone based on a violation of expectancy for a group of six stimuli that has been developed by primitive auditory intelligence. While the paradigm has been validated in healthy controls, to date it has not been used to study auditory change detection in early phase schizophrenia.

It is important to study early phase psychosis in order to treat patients as early as possible, and recent research has shown that individuals with early phase psychosis can provide information for intervention prior to development of full blown psychosis (Manzanas et al., 2014). The current study compared MMN data between early phase psychosis patients and healthy controls while using the complex pattern MMN paradigm. Based on previous research, it is hypothesized that complex pattern auditory change detection (as expressed by MMN) will be reduced in early phase psychosis patients compared to healthy controls.

2. Methodology

2.1. Participants

2.1.1. Clinical participants—Thirteen individuals (9 males) with early phase psychosis (EP) were recruited for this study from the Nova Scotia Early Psychosis Program (NSEPP). All clinical participants presented with a primary diagnosis of schizophrenia and had experienced their first psychotic break within the past five years (illness duration range: 6 mos.–5 years).

All clinical participants were between the ages of 19–40 years ($M = 24.7$ years; $SE = 1.2$) and were excluded if they met any of the following criteria: co-morbid DSM-IV Axis I disorder; total PANSS score >65 (reflecting an acute psychotic episode); current history of drug abuse or dependence; history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurological disorder; electro-convulsive therapy (ECT) treatment resulting in movement disorders which could affect ERP recordings; or abnormal hearing (as per self-report). Participant demographics are listed in Table 1.

2.1.2. Control participants—Fifteen healthy controls (HC), 9 males, between the ages of 19–40 years ($M = 26.9$; $SE = 2.2$) were recruited from the general public and had to meet the following inclusion criteria: no psychiatric, neurological, or alcohol/drug abuse history, with non-use of medication (other than oral contraceptives). HCs were matched as closely as possible to the clinical group with respect to age and gender. Patients and controls did not significantly differ on age or years of education.

2.2. Procedure

Prior to the day of the study, EPs were administered the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al., 1989) by a trained clinician at the NSEPP. Additionally, patients were administered the Auditory Hallucination Subscale of the Psychotic Symptom Rating Scale (PSYRATS; Haddock et al., 1999) by the study supervisor (DF).

Participants were asked to abstain from recreational drugs, alcohol and medications (with the exception of antipsychotics, adjunct drugs, and oral contraceptives) beginning at

midnight of the day they participated. Participants were not asked to abstain from nicotine substances as nicotine use is often elevated in schizophrenia patients due to its pro-cognitive effects (Fisher et al., 2012), and having smoking participants abstain prior to the study could promote serious withdrawal symptoms which could interfere with ERP recordings. Additionally, acute nicotine administration appears to have minimal effects on MMN amplitude (Fisher et al., 2012).

Upon arrival at the laboratory, participants provided informed consent before completing a screening questionnaire and a handedness questionnaire (Oldfield, 1971), following which electrodes were applied for the recording of electrophysiological data. Participants watched a silent movie of their choice and were asked to do their best to ignore the auditory stimuli, which were presented binaurally through ear inserts (Etymotic Research, Inc., Elk Grove Village, IL, USA). The procedure took approximately 1.5 h from set-up to completion. All study procedures were reviewed by the University Research Ethics Board at Mount Saint Vincent University as well as the Research Ethics Board of the Capital District Health Authority (CDHA).

2.3. Neurophysiological testing

Participants were presented a complex pattern (CP) MMN paradigm (Salisbury, 2012) in one ten minute block. The stimuli were 400 groups of six tones (1000 Hz, 75 dB, 50 ms duration, 330 ms stimulus onset asynchrony [SOA]), which was presented with an inter-trial interval (ITI) of 750 ms. Occasionally a group contained a deviant, meaning it was missing either the 4th or 6th tone (50 trials each). In these cases, there was a silent pause in place of where the 4th or 6th tone should be (as in Salisbury, 2012). For recording and analysis purposes, a distinct trigger was sent and recorded at the exact time that a tone would be expected. The paradigm is illustrated in Fig. 1.

2.4. EEG recording and ERP computation

Electrical activity was recorded using BrainVision Recorder software and a BrainVision BrainAmp MR amplifier (Brain Products GmbH, Munich, DE) with bandpass settings of 0.1 and 100 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer 2 software. ERPs were extracted from EEG activity recorded from an electrode cap with Ag+/Ag + Cl-ring electrodes at fifteen scalp sites placed according to the 10–20 system of electrode placement, including: three midline sites (frontal [FZ], central [CZ], parietal [PZ]); three left hemisphere (frontal [F3], central [C3], parietal [P3]); and three right hemisphere (frontal [F4], central [C4], parietal [P4] scalp sites and right mastoid (TP10)). Electrodes were also placed on the supra-/suborbital and external canthi sites for bipolar recordings of vertical (VEOG) and horizontal (HEOG) electro-oculogram activity, respectively, as well as on the tip of the nose (reference) and the mid-forehead (ground).

Electrical epochs (350 ms duration, beginning 50 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using an algorithm operating in the time and frequency domain (Gratton et al., 1983) and then baseline corrected using a 50 ms window of prestimulus electrical activity. Those epochs with EEG or EOG voltages exceeding ± 75 μ V were excluded from the analysis and the remaining artifact-free epochs were separately

averaged for each stimulus type and digitally filtered offline with a bandpass of 0.1 to 20 Hz.

For each site and deviant type, MMN waveforms were assessed by quantifying mean activity (± 8 ms) relative to baseline around peak negativity amplitudes within a custom-tailored window (100–250 ms) derived from an inspection of the grand-averaged waveform from each condition. For the deviants, electrical epochs were time locked to the trigger emitted at the expected onset of the missing stimuli. Unlike typical MMN paradigms, no difference waves (e.g. deviant-minus-standard) were generated as the MMN was elicited by the absence of sound, negating the need for such a subtraction as there is no afferent activity from non-adapted sensory cells to account for.

2.5. Data analysis

Analysis of main effects and interactions for each deviant type incorporated 2 within subjects factors: region (two levels; frontal [FZ, F3, F4] vs. central [CZ, C3, C4]) and laterality (three levels; left hemisphere vs. midline vs. right hemisphere), and one between subjects factor: EPs vs. HCs.

Data from the missing 4th and 6th stimuli were analyzed separately using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY). MMN amplitudes for each deviant were subjected to repeated-measures analysis of variance (ANOVA) procedures. Correlational Spearman's rho analyses (two-tailed) were performed to examine the relationship between MMN amplitudes and several demographic/clinical variables in EPs. These included age, illness duration, PANSS scores, PSYRATS scores, as well as antipsychotic dosage levels, which were translated into standardized chlorpromazine equivalent dosage levels (CPZ). Spearman's rho was specifically chosen due to the small sample size as well as its relative resistance to outlier effects.

3. Results

3.1. MMN amplitude

Results for the missing 4th stimulus showed a main effect of group, $F(1, 26) = 13.19$, $p = .001$, due to significantly larger MMN amplitudes for HCs ($M = -1.42 \mu V$, $SE = .35$) compared EPs ($M = .46 \mu V$, $SE = .38$). Planned pairwise comparisons for the missing 4th MMN revealed amplitudes to be larger in HCs compared to EPs at both frontal ($p < .001$) and central ($p = .017$) regions; more specifically, HC MMN amplitudes were larger than those of EPs at F3 ($p < .001$), FZ ($p = .001$), F4 ($p = .004$), C3 ($p = .008$), CZ ($p = .051$), and C4 ($p = .024$). Specific amplitude values are listed in Table 2, while waveforms are illustrated in Fig. 2.

Results for MMNs elicited by the missing 6th stimulus showed a main trend for group, $F(1, 26) = 3.44$, $p = .075$. Planned pairwise comparisons for the missing 6th MMN revealed frontal amplitudes to be larger in HCs compared to EPs ($p = .036$), specifically at sites F3 ($p = .046$) and FZ ($p = .027$). Specific amplitude values are listed in Table 2, while waveforms are illustrated in Fig. 3.

3.2. MMN latency

There were no significant main or interaction effects found for MMN latency elicited by either the missing 4th or missing 6th stimulus. Latency values are listed in Table 2.

3.3. Correlations

Correlational analysis of MMN amplitudes and clinical scores revealed the missing 4th MMN amplitudes to be positively correlated (i.e. as score increased, MMN decreased) with PSYRATS scores at C3 ($\sigma = .57$, $p = .043$), C4 ($\sigma = .55$, $p = .050$) and CZ ($\sigma = 0.61$, $p = .027$). There were no significant correlations found between demographic/clinical measures and MMN elicited by the missing 6th stimulus.

4. Discussion

In this study, we compared auditory change detection (as indexed by MMN) between early phase psychosis patients and healthy controls using a complex pattern MMN paradigm. To our knowledge, this is the first study to assess MMN in an early phase psychosis population using an abstract pattern paradigm, and, more specifically, the complex pattern MMN paradigm developed by Salisbury (2012).

It was hypothesized that we would find MMN amplitudes to be reduced in EPs when compared to HCs. The results for both the missing 4th and missing 6th stimuli supported this hypothesis as EPs were found to have significantly smaller MMN amplitudes than healthy controls. This is consistent with previous reports in early phase patients using a traditional auditory oddball MMN paradigm (Bodatsch et al., 2011; Atkinson et al., 2012; Kaur et al., 2013). These findings suggest that while HCs were able to recognize and group the pattern of six tones according to the gestalt principle of proximity, early phase psychosis patients were unable to do so (as reflected by the reduced, if not absent, MMN to missing tones). While this corroborates similar findings of a reduced MMN (vs. HCs) elicited by an identical paradigm in chronic schizophrenia patients (Salisbury, submitted), it suggests that the deficit can be seen within the early phase period, particularly for the missing 4th stimulus.

The reduced ability to form such perceptual groupings and respond to violations of the expected pattern has important implications in understanding early processing deficits in schizophrenia, which have been suggested to contribute to later cognitive and behavioral dysfunction (Javitt, 2009; Salisbury et al., 2010). Previously, Michie (2001) suggested that the cortical dysfunction in schizophrenia is more sensitive to duration (vs. pitch) deviants as the processing of duration deviants requires more intricate cortical computations, including those related to stimulus timing. Our current findings, elicited by a paradigm where the detection of violations in a pattern depends on cortical timing processes to group the pattern of tones together, corroborate the assertion that deviants requiring time estimation may be better trait-related measures of schizophrenia, particularly as these deficits in demanding cortical computations can be observed in the early phase of the illness.

There were no significant correlations found for the missing 6th stimulus; however correlational analyses done on brain activity elicited by the missing 4th stimulus found

increased PSYRATS scores (which quantify trait-related aspects of auditory hallucinations) to be associated with a smaller MMN. This is consistent with previous studies which have reported reductions of MMN amplitude to be associated with increased positive symptoms in general (Fisher et al., 2011; Fisher et al., 2014) and, more specifically, increased measures of hallucinatory trait (such as the PSYRATS; Hirayasu et al., 1998; Fisher et al., 2011; Youn et al., 2002). This is the first study, however, to demonstrate an association between AHs and cortical processing deficits so early in illness progression. These findings suggest that the previously observed differences are not solely seen in chronic patients, but appear to be present from illness onset. That said, there are several important differences between these previous studies and our current results, including the paradigm used, i.e. use of simple feature-change paradigms with alterations observed to frequency MMN (Hirayasu et al., 1998; Youn et al., 2002), duration MMN (Fisher et al., 2011) and novelty MMNi (Fisher et al., 2014) vs. a complex pattern paradigm. It remains to be seen whether the association between auditory hallucinations and MMN in early phase psychosis can be observed with more traditional paradigms, or whether a complex paradigm, such as the one used in this study, is necessary to probe this relationship between symptoms and cortical function.

Further analysis was done to examine the impact of illness duration on MMN scores, as changes in MMN across the early phase of schizophrenia have previously been reported (Salisbury et al., 2007). MMNs elicited by this paradigm seem to be relatively unaffected by illness duration within EP, suggesting that MMN elicited by this complex pattern paradigm is impaired from illness onset. Given the suggestion that paradigms which probe higher order processes may be more appropriate for elucidating subtle auditory change detection deficits early in the progression of psychosis (Salisbury, 2012), and the finding that these observed MMN deficits are unaffected by illness duration in this EP population, future studies should follow up these findings to determine if the MMN elicited by this complex pattern paradigm is impaired in prodromal and ultra high-risk individuals and, specifically, whether it has any predictive utility in determining who is likely to convert to psychosis. If future studies were able to demonstrate reliable and specific prediction of conversion in high-risk individuals, this would have immeasurable utility in identifying patients who would benefit from early intervention before they progress into a first psychotic episode, thereby improving future quality of life.

In conclusion, we found significant differences between early phase psychosis patients and healthy controls with regard to MMNs elicited by complex pattern paradigm that requires auditory grouping. While similar findings in early phase psychosis, as well as in the psychosis prodrome, have been reported with simple feature-change stimulus paradigms (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2011; Atkinson et al., 2012; Kaur et al., 2013), these findings have not been replicated elsewhere (Salisbury et al., 2002, 2007; Umbricht et al., 2006; Magno et al., 2008). It is our hope that this complex pattern MMN paradigm may lead to more consistent and robust findings in this population. This paradigm may target a key deficit in schizophrenia that is subtle in the early phase of the illness and, therefore, may serve as an important biomarker of disease-related pathophysiology.

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Fig. 1. Schematic illustration of the complex pattern MMN paradigm (adapted from Salisbury, 2012). All tones were at a pitch of 1000 Hz and a duration of 50 ms. The interval between tone groupings was 750 ms.

Fig. 2. Grand averaged missing 4th MMN waveforms for early phase psychosis (EP) and healthy controls (HC) at frontal (F₃, F_Z, F₄) and central (C₃, C_Z, C₄) electrode sites.

Fig. 3. Grand averaged missing 6th MMN waveforms for early phase psychosis (EP) and healthy controls (HC) at frontal (F₃, F_Z, F₄) and central (C₃, C_Z, C₄) electrode sites.

Table 1

Mean ($\pm$ SE) participant demographics for early-phase psychosis patients (EP) and healthy controls (HC).

	HC	EP
Age	26.40 (1.96)	24.83 (1.30)
Years of education	16.57 (0.95)	14.17 (0.87)
Illness duration	–	3.06 (0.90)
PANSS positive	–	12.17 (2.03)
PANSS negative	–	13.25 (1.76)
PANSS general	–	26.58 (2.68)
PSYRATS	–	5.25 (3.07)
Medication dosage (chlorpromazine equivalents)	–	164.75 (18.78)

Table 2

Mean MMN amplitudes and latencies elicited by the missing 4th (M4) and missing 6th (M6) stimuli for early for early-phase psychosis patients (EP) and healthy controls (HC).

	M4		M6	
	HC	EP	HC	EP
F ₃	−1.58 μ V	.48 μ V	−1.41 μ V	−.47 μ V
F _Z	−1.76 μ V	.28 μ V	−1.72 μ V	−.54 μ V
F ₄	−1.43 μ V	.31 μ V	−1.44 μ V	−.30 μ V
C ₃	−1.15 μ V	.62 μ V	−1.14 μ V	−.35 μ V
C _Z	−1.22 μ V	.52 μ V	−1.35 μ V	−.51 μ V
C ₄	−1.38 μ V	.56 μ V	−.83 μ V	−.33 μ V
Latency (at F _Z)	189.07 ms	186.17 ms	159.6 ms	165.0 ms