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Mismatch negativity-indexed auditory change detection of speech sounds in early and chronic schizophrenia

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ABSTRACT

Auditory change detection, as indexed by the EEG-derived mismatch negativity, has been demonstrated to be dysfunctional in chronic schizophrenia using both pure-tone and speech (phoneme) sounds. It is unclear, however, whether reduced MMN amplitudes to speech sound deviants are observed within the first 5 years of the illness. The present study investigated MMNs elicited by across-vowel (phoneme) change in early schizophrenia (ESZ; Experiment 1) as well as chronic schizophrenia (CSZ; Experiment 2). In both experiments, clinical and control participants were presented the Finnish phoneme /e/ (standard; $P = .90$) and the Finnish phoneme /ö/ (deviant; $P = .10$) within an oddball paradigm. In experiment 2 we report significantly reduced MMN amplitudes in CSZ relative to HCs, but no differences were found when comparing ESZ and HC in experiment 1. Additionally, in our clinical samples, MMN amplitudes were correlated with symptom scores. These findings suggest that early detection of phonetic change may be impaired in chronic schizophrenia, but not early in the progression of the illness. As MMN reductions only emerged in patients with a longer course of illness, and appeared to change with symptom severity, this suggests a dynamic change in the early auditory processing of language over time in schizophrenia.

1. Introduction

Schizophrenia (SZ) is a uniquely debilitating brain disease (DeLisi, 2008), typically emerging in early adulthood and affecting just below 1% of the world's population (Kahn et al., 2015). SZ is known to be associated with progressive social and functional decline for many during the early course of the disease, and peri-onset progressive pathology and pathophysiology have been demonstrated (Kasai et al., 2003; Salisbury et al., 2007). Early-phase schizophrenia is the critical phase within five years of an individual's first psychotic break (Larsen et al., 2011). During this time period some will recover, while others will go on to exhibit a chronic form of the disease (Jaaskelainen et al., 2013).

One of the most efficient ways to probe cortical functioning is with the electroencephalogram (EEG). The EEG can assess the cognitive and perceptual processing in the brain through the non-invasive measurement of neuroelectric brain activity at the scalp. One EEG-derived event-related potential (ERP) component, the auditory mismatch negativity (MMN), is thought to reflect the detection of change among stimulus constancies in the environment; due to the basic and automatic nature of this process, the MMN has been conceptualized as a probe of central auditory function (Näätänen et al., 2011). The MMN is commonly generated by randomly inserting rare deviant auditory stimuli into a train of standard stimuli, with the deviant differing from the standard by any detectable change (including frequency, duration, or intensity, or even speech sounds) (Näätänen and Alho, 1997).

Chronic schizophrenia is commonly associated with deficits in basic auditory information processing, as reflected in the consistent reports of robust MMN amplitude reductions (Coffman et al., 2017; Ford et al., 2010; Javitt et al., 1993; Shelley et al., 1991; Todd et al., 2008) especially to duration deviants (Michie, 2001). Notably, reductions in MMN appear to be unique to schizophrenia among disorders of psychosis (Catts et al., 1995; Salisbury et al., 2007; Umbricht et al., 2003). A recent meta-analysis investigating MMN deficits in first-episode

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psychosis reported no effect in MMNs elicited by frequency deviants, and a small-to-medium effect when duration deviants were used (Haigh et al., 2017), while another meta-analysis reported first episode patients to exhibit a reduced MMN compared to healthy controls, but with a significantly smaller effect size relative to those with chronic schizophrenia (Erickson et al., 2016). Both of these meta-analyses, however, only considered MMNs elicited by pure tone stimuli.

Instead of the more common pure-tone paradigms, phonetic paradigms use speech sounds. While there is a wealth of studies that have employed MMNs elicited by speech sounds to probe language-based processes in healthy and clinical populations (Aaltonen et al., 1987; Dehaene-Lambertz et al., 2000; Friederici et al., 2002; Rinne et al., 1999; Sussman et al., 2004), with many employing phonemes (i.e. the simplest unit of speech with linguistic meaning) as standard and deviant stimuli, few have been conducted in the context of schizophrenia. Kasai and colleagues (Kasai et al., 2002) reported significant deficits in MMN amplitudes SZ patients when compared to healthy controls in response to across-phoneme change (Japanese vowel /a/ vs. Japanese vowel /o/; Kasai et al., 2002). This study was replicated in English-speaking SZ patients, with a significant reduction in MMN amplitudes reported in the patient sample (vs. controls) (Fisher et al., 2008a). Deficits in the detection of phonetic change have important behavioral and neurological consequences; phonetic MMN and MMNm (the magnetic equivalent) deficits have been associated with poorer auditory verbal memory in schizophrenia (Kawakubo et al., 2006), and has been shown to be correlated with reduced left planum temporale grey matter volume (Yamasue et al., 2004). Notably, of the few studies that have probed auditory change detection using phonemes in schizophrenia, none have examined this phenomenon early in the illness.

The current study assessed MMN-indexed auditory change detection of phoneme stimuli in early schizophrenia (ESZ) patients, chronic schizophrenia (CSZ) patients, and healthy controls. We replicated Näätänen et al.'s (1997) methods, employing Finnish phonemes to elicit MMNs in our English-language speaking sample. As MMN enhancement to phonemes within the native language due to the activation of long-term memory processes (Dehaene-Lambertz, 1997; Näätänen et al., 1997; Sharma and Dorman, 1999) have been reported, Finnish vowels were used in order to isolate 'pure' change-detection processes and minimize the influence of previous language learning. We did, however, choose easily discriminable vowels, as per Winkler et al.'s (1999) findings that MMN is abolished when participants cannot distinguish between phonemic stimuli. Based on previous findings of robust MMN deficits, we hypothesized that MMN will be reduced in CSZ participants compared to healthy controls. We also hypothesized that MMNs would be reduced in ESZ participants (relative to controls), albeit to a lesser degree than that observed in CSZ. A secondary hypothesis of this study was that MMN amplitudes would be correlated with positive, negative and general symptom severity, such that increased symptoms would be associated with reduced MMN amplitudes. This hypothesis is consistent with previous reports of MMN amplitudes being reduced in schizophrenia patients with increased symptoms, both in chronic (Fisher et al., 2012b, 2014; Oades et al., 1996) and early psychosis (Ells et al., 2018; Rudolph et al., 2015) populations.

2. Methods

2.1. Experiment 1 – Early schizophrenia

2.1.1. Clinical participants

Thirteen (6 female) early schizophrenia (ESZ) patients were recruited from the Nova Scotia Early Psychosis Program (NSEPP), an early intervention service for psychosis. All patient participants were diagnosed with SZ using DSM criteria by their treating psychiatrists and were within 5 years of illness onset. ESZ participants were administered the Positive and Negative Symptom Scale for schizophrenia (PANSS) (Kay et al., 1989) by a member of the treatment team, as per standard care procedures. Additionally, patients were administered the Auditory Hallucination Subscale of the Psychotic Symptom Rating Scale (PSYRATS) (Haddock et al., 1999), by the PI (DF), which was used to quantify trait-related aspects of auditory hallucinations.

Table 1
Mean (± SD) age, years of Education, PANSS subscale scores, score on the auditory hallucinations subscale of the Psychotic Symptoms Rating Scale (PSYRATS), and medication dosage (in chlorpromazine equivalents) for early schizophrenia (ESZ), chronic schizophrenia (CSZ) and healthy control (from both experiment 1 and experiment 2) samples.

	ESZ – Exp. 1	CSZ – Exp. 2	HC – Exp. 1	HC – Exp. 2
Age	25.23 (3.81)	29.09 (5.94)	26.40 (6.20)	27.36 (5.20)
Years of Education	14.26 (2.34)	12.39 (1.83)	16.57 (2.51)	15.00 (1.73)
Years of Illness	2.42 (1.40)	6.58 (1.51)	–	–
PANSS Positive	10.69 (4.80)	15.50 (5.32)	–	–
PANSS Negative	12.46 (6.17)	20.50 (7.34)	–	–
PANSS GP	25.38 (8.72)	33.25 (9.25)	–	–
PSYRATS	3.92 (7.66)	18.70 (15.55)	–	–
Dosage (CPZ)	164.35 (66.64)	282.14 (77.34)	–	–

All participants were judged as clinically stable for the four weeks prior to testing by their primary physician (i.e., no significant changes in medications or symptoms), had primary medication limited to one of the atypical anti-psychotics, and understood spoken and written English. Participant demographics are summarized in Table 1.

Exclusion criteria were as follows: current drug dependence or abuse; previous loss of consciousness due to a head injury, a co-morbid DSM-IV TR Axis I disorder, diagnosis of epilepsy or any other neurologic disorder, electro-convulsive therapy (ECT) treatment within the previous year, extrapyramidal symptoms (EPS) that result in movement disorders (which could affect ERP recordings), or self-reported hearing difficulties.

2.1.2. Control participants

Fourteen (4 male) healthy control (HC) participants were recruited from the general public. All HCs self-reported no psychiatric, neurological and/or alcohol/drug abuse histories, no first degree relatives with a diagnosis of psychosis, and no current use of medications (excluding oral contraceptives). Patients and controls did not significantly differ on age or years of education. Demographics are presented in Table 1.

2.1.3. Study procedure

All recordings were done at the BIOTIC Neuroimaging Research Laboratory located at the QEII Health Sciences Centre in Halifax, NS. 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. Tobacco-using participants were not asked to abstain from nicotine substances as abstinence could promote withdrawal symptoms that could interfere with ERP recordings. Additionally, acute nicotine administration (e.g. smoking prior to data collection) appears to have minimal effects on MMN amplitude in both patient and control populations (Fisher et al., 2012a; Inami et al., 2005, 2007).

Upon arrival at the laboratory, participants provided informed consent before completing a screening questionnaire, following which electrodes were applied for the recording of electrophysiological data. After EEG hookup, participants viewed a muted movie of their choosing and were asked to sit as still as possible while ignoring the auditory stimuli. The procedure took approximately 1.5 h from set up to completion.

Study procedures were conducted following the principles of the Declaration of Helsinki and following ethics approval by the Research Ethics Board of the Capital District Health Authority (File #: CDHA-RS/

2013-120) as well as the University Research Ethics Board of Mount Saint Vincent University (File #: 2012-033).

2.1.4. Phonetic auditory oddball MMN paradigm

MMNs were elicited in response to across-phoneme (vowel) change (standard vowel /e/: 400 ms duration, deviant vowel /ö/: 400 ms duration) using identical semi-synthetic vocal stimuli to those used by Näätänen et al. (1997). The standard phoneme is akin to the cardinal vowel /e/ of the International Phonological Alphabet (IPA); the deviant vowel /ö/ is described as being half-way between the IPA [ø] and [œ] and is phonologically distinct from the standard (Suomi et al., 2008). The two phonemes differ only in second-formant (F2) frequency, with consistent fundamental (f0), F1, F3 and F4 frequencies (Näätänen et al., 1997; Suomi et al., 2008) thereby controlling for the impact of large phonological differences impacting neural response while still being easily differentiated. All 1200 stimuli were presented at an intensity of 75 dB sound pressure level, with a 10 ms fall and rise time. The average fundamental frequency of each semi-synthesized vowel was 105 Hz. Standard and deviant probabilities were 90% and 10% respectively and stimuli were presented in a pseudo-randomized order (such that two deviants did not occur within 2 stimuli of each other) with a stimulus-onset asynchrony of 400 ms with a randomly occurring SOA variability of 50 ms. The stimuli were presented binaurally through EAR 3A insert earphones (Etymotic Research Inc., Elk Grove Village, IL).

2.1.5. EEG recording and computation

Electrical activity was recorded from an electrode cap with Ag^+/Ag^+Cl^- ring electrodes at fifteen scalp sites according to the 10–20 system of electrode placement using BrainVision Recorder software and a BrainVision BrainAmp MR amplifier (Brain Products GmbH, Munich, DE). 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). A nose reference was used to allow for visual inspection of MMN inversion at mastoids. EEG activity was amplified with bandpass settings of 0.1–100 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer 2 software. All impedences were kept below 10 kΩ.

Prior to ERP analysis, electrical activity was separately averaged for each stimulus type (i.e. standards vs. deviants) and was digitally filtered offline with a bandpass of 0.15–20 Hz. Electrical epochs (350 ms duration, beginning 50 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using an algorithm operating in the time and frequency domain (Gratton et al., 1983) and then baseline corrected using a 50 ms window of prestimulus electrical activity. Those epochs with EEG or EOG voltages exceeding ± 75 μV were excluded from the analysis and the remaining artifact-free epochs were averaged according to stimulus type. The mean number of stimuli included in standard and deviant averages for each group are listed in Table 2.

MMN difference waveforms were computed by a digital point-by-point subtraction of the standard stimulus values from those values that were elicited by the deviant stimulus. Peaks were assessed by quantifying the peak negative amplitudes (in relation to the average baseline activity pre-stimulus). Output was the average electrical activity within four voltage points (8 ms) to the left and right of the peak amplitude. MMN latency measurements were taken at F_Z, which is the site of maximum amplitude.

2.1.6. Data analyses

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS 23; IBM Corp., Armonk NY). MMN amplitudes measured from the difference wave were subjected to repeated-measures analysis of variance (ANOVA) procedures with one between-group (2 levels: ESZ, HC) and two-within group factors (laterality [left, midline, right], and region [limited to the frontal (F) and central (C) regions]). *A priori* planned comparisons of between-group differences were conducted for MMN amplitudes at frontal sites (F_3, F_Z, F_4). Where appropriate, effect sizes for pairwise comparisons were reported using Hedges' *g* to account for the relatively small sample size. A two-tailed independent samples *t*-test was also performed to assess potential group differences in MMN latency. Additionally, Spearman's rho (ρ) correlational analyses were performed to examine the relationship between MMN amplitudes at frontal sites and correlates of illness (duration of illness, symptoms ratings taken from the PANSS and PSYRATS, standardized antipsychotic dosage measured in chlorpromazine equivalents).

2.2. Experiment 2 – Chronic schizophrenia

2.2.1. Clinical participants

Twelve (2 female) chronic schizophrenia (CSZ) patients were recruited from the Schizophrenia Clinic of the Royal Ottawa Mental Health Centre. All patient participants were diagnosed with SZ using DSM-IV-TR criteria by their treating psychiatrists, using the SCID-I/P (First and Pincus, 2002), and had a duration of illness of at least 5 years. Symptom severity was measured with the PANSS (Kay et al., 1989), administered by the patient's physician. Additionally, patients were administered the Auditory Hallucination Subscale of the PSYRATS (Haddock et al., 1999) by the PI (DF), which was used to quantify trait related aspects of auditory hallucinations.

Apart from where noted above, inclusion and exclusion criteria for CSZ patients were identical to Experiment 1. Participant demographics are summarized in Table 1.

2.2.2. Control participants

Eleven (2 female) HC participants were recruited from the general public. Inclusion and exclusion criteria for HCs were identical to Experiment 1. Patients and controls did not significantly differ on age, but did differ on years of education (t (16) = −3.11, p = .007).

Table 2
Mean (± SD) MMN latency (ms) at F_Z and amplitudes (μV) at frontal (F_3, F_Z, F_4) and central (C_3, C_Z, C_4) electrode sites for early schizophrenia (ESZ), chronic schizophrenia (CSZ) and healthy control (from both experiment 1 and experiment 2) samples.

	ESZ	CSZ	HC – Exp. 1	HC – Exp. 2
Latency	198.77 (54.70)	184.67 (39.72)	192.85 (32.44)	170.72 (32.53)
F_3	−2.55 (1.23)	−0.95 (1.00)	−2.69 (1.22)	−2.46 (1.11)
F_Z	−2.75 (1.18)	−1.34 (1.16)	−3.49 (1.38)	−2.73 (0.79)
F_4	−2.47 (1.08)	−0.96 (0.88)	−3.20 (1.45)	−2.60 (0.89)
C_3	−2.32 (1.08)	−0.24 (0.67)	−2.21 (1.62)	−1.00 (1.04)
C_Z	−2.71 (1.24)	−0.89 (0.76)	−2.88 (2.14)	−1.41 (0.93)
C_4	−2.23 (1.38)	−0.66 (1.01)	−2.44 (1.84)	−1.25 (0.82)
# Stimuli included in average - standard	780.38 (71.25)	795.25 (105.64)	781.21 (81.91)	828.18 (31.63)
# Stimuli included in average - Deviant	68.46 (10.54)	82.25 (13.66)	67.78 (11.98)	83.82 (10.91)

2.2.3. Study procedure

Study procedures were identical to Experiment 1 with the exception that all recordings were done at the Royal Ottawa Mental Health Centre.

The study was conducted according to the principles of the Declaration of Helsinki and following approval of both the Research Ethics Board of the Royal Ottawa Health Care Group and the Carleton University Ethics Committee for Psychological Research.

2.2.4. Phonetic auditory oddball MMN paradigm

Task stimuli were identical to Experiment 1.

2.2.5. EEG recording and ERP computation

Identical to Experiment 1, with the following exception: electrical activity was recorded from an electrode cap with Ag^+/Ag^+Cl^- ring electrodes at 32 scalp sites according to the 10–20 system of electrode placement using BrainVision Recorder software and a BrainVision QuickAmp 40 amplifier (Brain Products GmbH, Munich, DE).

2.2.6. Data analyses

Data analyses were identical to Experiment 1.

3. Results

3.1. Experiment 1 - Early schizophrenia

3.1.1. MMN amplitude

Results showed a main effect of region, F (1,25) = 4.90, p = .036, partial ε^2 = 0.16, due to significantly larger MMN amplitudes at frontal (vs. central) regions. No significant between-group differences for main effects or interactions. Additionally, planned comparisons of between group differences at frontal electrode sites reported no significant differences between group at F_3 (p = .76; Hedges' g = 0.12), F_Z (p = .15; Hedges' g = 0.58) or F_4 (p = .15; Hedges' g = 0.57). Mean amplitudes (± SD) are summarized in Table 2; MMN waveforms are illustrated in Fig. 1.

3.1.2. MMN latency

There was no significant difference between groups for MMN latency (p = .73; Hedges' g = 0.13).

3.1.3. Correlations

There were no significant correlations at frontal electrode sites.

3.2. Experiment 2 – Chronic schizophrenia

3.2.1. MMN amplitude

Results showed a main effect of region, F (1,21) = 26.90, p < .001, partial ε^2 = 0.56, due to larger overall amplitudes at frontal (vs. central) sites. A main effect of group was observed, F (1,21) = 16.04, p = .001, partial ε^2 = 0.43, due to larger overall MMN amplitudes for the HC group (M = −1.93 μV, SE = 0.20) compared to CSZs (M = −0.84 μV, SE = 0.19). Finally, there was also a significant group x region interaction, F (1,21) = 5.33, p = .031, partial ε^2 = 0.20. Follow-up of this interaction revealed HCs to have larger MMN amplitudes at both frontal (p = .001) and central (p = .015) regions. Further analyses involving site found HCs to have larger MMN amplitudes compared to CSZs at F_3 (p = .002; Hedges' g = 1.38), F_Z (p = .004; Hedges' g = 1.63) and F_4 (p = .001; Hedges' g = 1.30) electrode sites, as well as at C_3 (p = .030; Hedges' g = 0.93). Due to the significant difference between groups on years of education, analyses were re-performed using years of education as a co-variate; overall, the pattern of results did not change (i.e.HC > CSZ at frontal sites), though the group difference at site C3 disappeared. Mean amplitudes (± SE) are summarized in Table 2; MMN waveforms are illustrated in Fig. 2.

3.2.2. MMN latency

There was no significant difference for MMN latency between CSZ and HC (p = .37; Hedges' g = 0.38).

3.2.3. Correlations

PANSS-GP scores were positively correlated (i.e. a symptoms increase, MMN decreases) with MMN amplitudes at sites F_3 (ρ = 0.72, p = .030) and F_Z (ρ = 0.87, p = .002)

3.3. Early vs. chronic schizophrenia

As both experiment 1 and experiment 2 were conducted using identical MMN paradigms, were analyzed in identical fashion and were recorded under extremely similar conditions (i.e. both recorded with Ag^+/Ag^+Cl^- electrodes and Brain Products amplifiers with identical sampling rates and bandpass filters), we compiled the patient data from the two experiments in an exploratory correlational analysis that was identical to the analyses performed with smaller samples in experiments 1 and 2. Prior to analyzing the data from clinical participants, in order to be sure of equivalence between recording sites, we first compared the data between our two healthy control samples. Our two HC samples did not differ on age or years of education. The two groups did not differ on MMN amplitudes at any of the 6 electrode sites (p > .05), nor did they differ in MMN latency.

3.3.1. MMN amplitude

There was a significant difference between the two groups on several clinical measures, including medication dosage (in chlorpromazine equivalents; p = .003), PANSS Positive Symptoms score (p = .046), PANSS Negative Symptoms scores (p = .014) and PSYRATS scores (p = .017).

A main effect was found observed for region, F (1,23) = 4.00, p = .032, partial ε^2 = 0.18, due to larger amplitudes at frontal (vs. central) sites. There was also a main effect of group, F (1,23) = 21.48, p < .001, partial ε^2 = 0.48, due to overall larger MMN amplitudes for ESZ (M = −2.50 μV, SE = 0.25) compared to CSZ participants (M = −0.84 μV, SE = 0.26). Follow-up of these effects revealed the larger amplitudes for ESZ participants to be observed at both frontal (p = .001) and central (p < .001) regions, as well as all electrode sites. Specifically, ESZ participants had larger amplitudes compared to CSZ participants at F_3 (p = .002; Hedges' g = 1.38), F_Z (p = .006; Hedges' g = 1.16), F_4 (p = .001; Hedges' g = 1.54), C_3 (p < .001; Hedges' g = 2.31), C_Z (p < .001; Hedges' g = 1.70), and C_4 (p = .004; Hedges' g = 1.25) electrode sites. Amplitudes for both groups are reported in Table 2; MMN waveforms are illustrated in Fig. 3.

3.3.2. MMN latency

There was no significant difference between groups for MMN latency.

3.3.3. Correlations

Spearman's rho correlations were performed in the combined SZ sample (i.e. ESZ + CSZ, n = 25) with stratified sampling, with group membership (ESZ vs. CSZ) as the strata variable to control for the effects of between-group differences on the correlations. Additionally, prior to conducting the correlations, a discriminant function analysis was performed to identify variables that allow for group prediction with high sensitivity and may confound correlational analyses with between-group differences. Using a step-wise model including the variables included in correlations for Experiments 1 and 2, illness duration and MMN amplitude at F_3 were included in predictive models. Specifically, model 1 (including only illness duration; Lambda = 0.321, p < .001) and model 2 (including both illness duration and MMN amplitude at F_3; Lambda = 0.134, p < .001) were significant predictors of group membership. As such, these variables were removed from the correlational analyses. We also conducted a comparison of correlations to

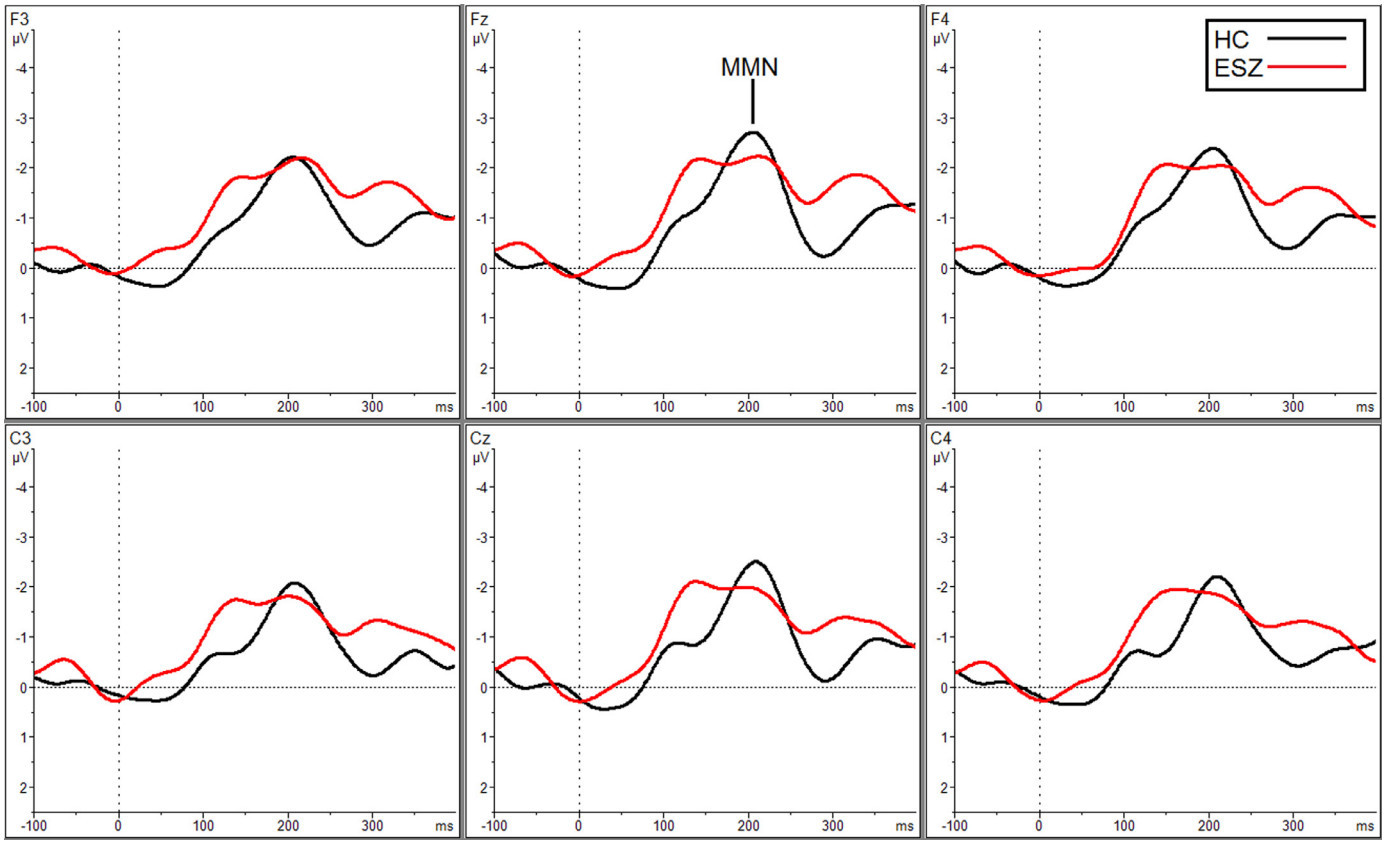

Fig. 1. Grand averaged MMN difference waves for early schizophrenia patients (ESZ) and healthy controls (HC) at frontal and central electrode sites. There was no significant difference between the groups at any sites ($p > .05$).

validate the combination of these two subgroups by performing a Fisher's r to z transformation and assessing whether there was a significant difference using an observed z-test statistic with the level of significance set at $\alpha = 0.05$ ($z_{critical} = \pm 1.96$). There were no significant differences between the sub-group correlation coefficients for any of the reported significant pooled correlations (i.e. $-1.96 < z < 1.96$, $p > .05$). For the combined SZ sample, significant Spearman's rho correlations found MMN amplitudes to be positively correlated with PANSS positive symptom scores at F_4 ($\rho = 0.48$, $p = .015$) and Fz ($\rho = 0.522$, $p = .007$), as illustrated in Fig. 4; and with PANSS GP scores at Fz ($\rho = 0.49$, $p = .021$). In all cases, the positive correlation indicated that increased symptoms scores were associated with a smaller (i.e. more positive) MMN.

4. Discussion

In this study, we investigated auditory change detection of speech sounds (as indexed by MMN) in early and chronic schizophrenia. To our knowledge, this is the first study to assess MMN elicited by speech sounds (phonemes) in an ESZ population, and one of very few to do so in a chronic schizophrenia population.

We hypothesized that phoneme MMN amplitudes would be reduced in participants with chronic schizophrenia, consistent with results using pure-tone stimuli, as well as the few studies in this population using speech-related stimuli (Fisher et al., 2008a; Kasai et al., 2002). The results supported this hypothesis as CSZs were found to have significantly smaller MMN amplitudes (vs. controls) at all three frontal sites examined. These results are consistent with previously reported findings of MMN deficits in schizophenia elicited by duration (Catts et al., 1995; Fisher et al., 2008b), frequency (Javitt et al., 1993; Umbricht et al., 2003), intensity (Fisher et al., 2008b; Todd et al., 2008), and combined "double" deviants (Hay et al., 2015; Perez et al., 2014) in pure-tone paradigms, as well as reduced MMN amplitudes (Fisher et al., 2008a; Kasai et al., 2002) or magnetoencephalographic source strength (Yamasue et al., 2004) elicited by speech sounds.

Despite the positive findings found within our CSZ group, there was no significant MMN amplitude reduction for our early schizophrenia participants relative to healthy controls (although a moderate effect size was observed at right and midline frontal electrodes). This is contrary to some reports of MMN deficits in early schizophrenia and early psychosis (Atkinson et al., 2012; Hay et al., 2015; Koshiyama et al., 2017; Nagai et al., 2013; Rydkjaer et al., 2017), but in line with others reporting no MMN-indexed deficit early in the illness (Magno et al., 2008; Mondragon-Maya et al., 2013; Salisbury et al., 2002; Umbricht et al., 2006). When compared directly to early schizophrenia participants, those in our chronic group still exhibited reduced MMN amplitude across all electrode sites. It is unclear whether this difference is due to "chronicity" of illness or severity, as the two groups significantly differed on all three PANSS subscales, as well as on a trait measure of auditory hallucination severity. The difference in MMN amplitudes between early and chronic schizophrenia samples has been previously reported with pure-tone stimuli, with chronic schizophrenia patients exhibiting the largest effects in a meta-analysis by Erickson et al., (2016). One variable that commonly confounds investigations of MMN across illness is age, as MMN amplitudes reduce with increasing age (Kiang et al., 2009). As there was no significant difference in age between our two clinical samples, the difference in MMN amplitudes must be due to illness severity, inclusion of participants with poorer outcomes in the CSZ group (Erickson et al., 2016) or some other factor.

It has been suggested that the less consistent MMN findings in early schizophrenia and early psychosis (relative to CSZ) are at least partially due to the makeup of the individual samples (Haigh et al., 2016). In the present study, our ESZ participants appeared to be less ill as evidenced

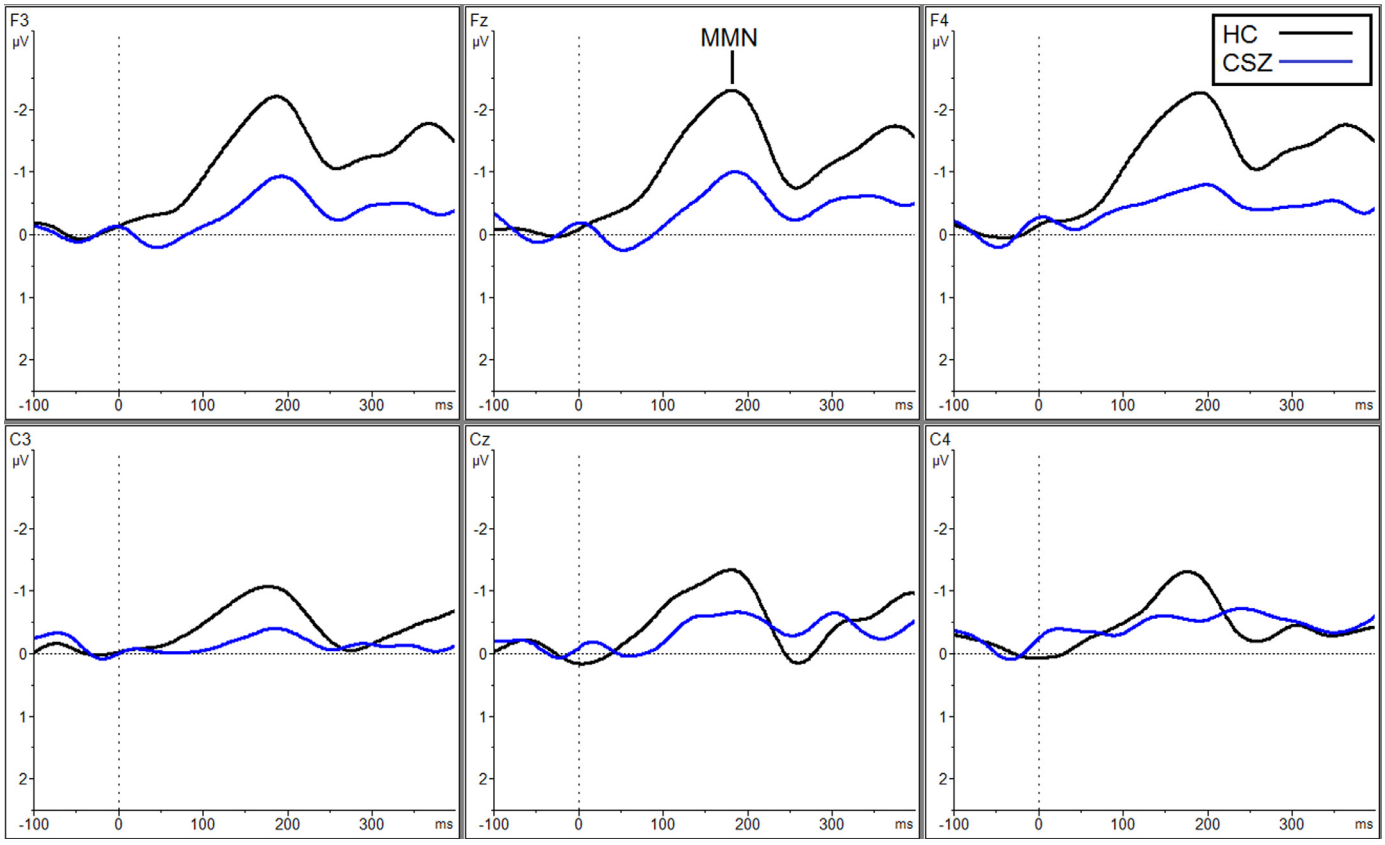

Fig. 2. Grand averaged MMN difference waves for chronic schizophrenia patients (CSZ) and healthy controls (HC) at frontal and central electrode sites. There was a significant difference between the groups at sites F_3, F_Z, F_4 and C_3 ($p < .05$).

by reduced PANSS scores relative to the samples in other studies reporting MMN deficits in early schizophrenia (Hay et al., 2015; Nagai et al., 2013). Conversely, it could be that phonemes in general are inappropriate to probe auditory change detection deficits in an early-phase population. As mentioned earlier, this is the first study to report MMN findings elicited by speech sounds in an ESZ sample, therefore there is no existing literature in this population to directly contrast our findings against. It could also be that the difference between the specific sounds used in this study was not cognitively taxing enough, and therefore not able to elucidate the subtle cognitive deficits present early in schizophrenia (Salisbury, 2012). Conversely, we might have been underpowered to detect this difference given the smaller effect size observed relative to that in our chronic schizophrenia sample.

What is unclear, however, based on these findings is whether MMN deficits progressively worsen over the course of the illness (Salisbury et al., 20072002), or whether degradation in the cortical processes underlying MMN occur within the early phase of the illness and then stabilize (i.e. non-linear progressive impairment), as suggested by the finding that duration of illness is unrelated to MMN amplitudes in chronic schizophrenia (Erickson et al., 2016). Unfortunately the present study is unable to answer this question due to its cross-sectional nature. Nonetheless, these results suggest that speech sounds are appropriate for elucidating MMN-indexed dysfunction in chronic schizophrenia, particularly for studies wanting to use stimuli with greater ecological validity. Additionally, they offer preliminary evidence that phoneme MMN-indexed function differs between those within the first five years of illness and those with more chronic forms of the illness.

Interestingly, MMN amplitudes were found to be positively correlated with PANSS positive symptom and general psychopathology scores (i.e. MMN decreases as symptom scores increase) in our combined ESZ and CSZ sample. It appears that the combined analysis brought forth associations that the analyses in our individual groups may have been too underpowered to elucidate. These correlations suggest that phoneme deviant-elicited MMN deficits increase as positive symptoms worsen, which is congruent with similar reports in chronic SZ patients using pure tone stimuli (Catts et al., 1995; Fisher et al., 2011b, 2014; Hirayasu et al., 1998; Youn et al., 2003). Additionally, MMN amplitudes have been found to be associated with positive symptoms in early phase psychosis, albeit in response to a complex pattern paradigm (Rudolph et al., 2015). Together, these findings provide further evidence of the link between the symptoms of psychosis and MMN deficits. It is unclear at this point, however, whether the association between symptoms and MMN amplitudes is driven by illness severity or something specific to the symptoms themselves. On one hand, symptom severity has been reported to be associated with decreased psychosocial function (Gur et al., 2015) and several studies have linked daily life function to deficits in MMN amplitude (Haigh et al., 2018; Light and Braff, 2005; Salisbury et al., 2017). Conversely, increases in auditory hallucination severity has been specifically linked to deficits in the MMN (Fisher et al., 2011a; Fisher et al., 2008b; Ford et al., 2012), with the suggestion that grey matter loss in and around Heschl's gyrus underlies both the increase in hallucinations and decrease in MMN amplitude (Salisbury et al., 2007). However, as suggested in a recent meta-analysis, it is unlikely that MMN deficits are correlated with positive symptoms or negative symptoms as a whole (Erickson et al., 2017). Future research with phoneme stimuli should attempt to link MMN amplitudes to more focused symptom measures in larger samples (vs. broader syndromes), and with an aim to elucidate the connection with specific symptoms, particularly those with known neurobiological underpinnings. While we attempted to control for the effects of between-group differences on our findings, the results of the correlations may be due in part to both differing stages of illness and symptom profiles between our groups. Of course, duration of illness and symptoms are often related. It has been previously suggested that

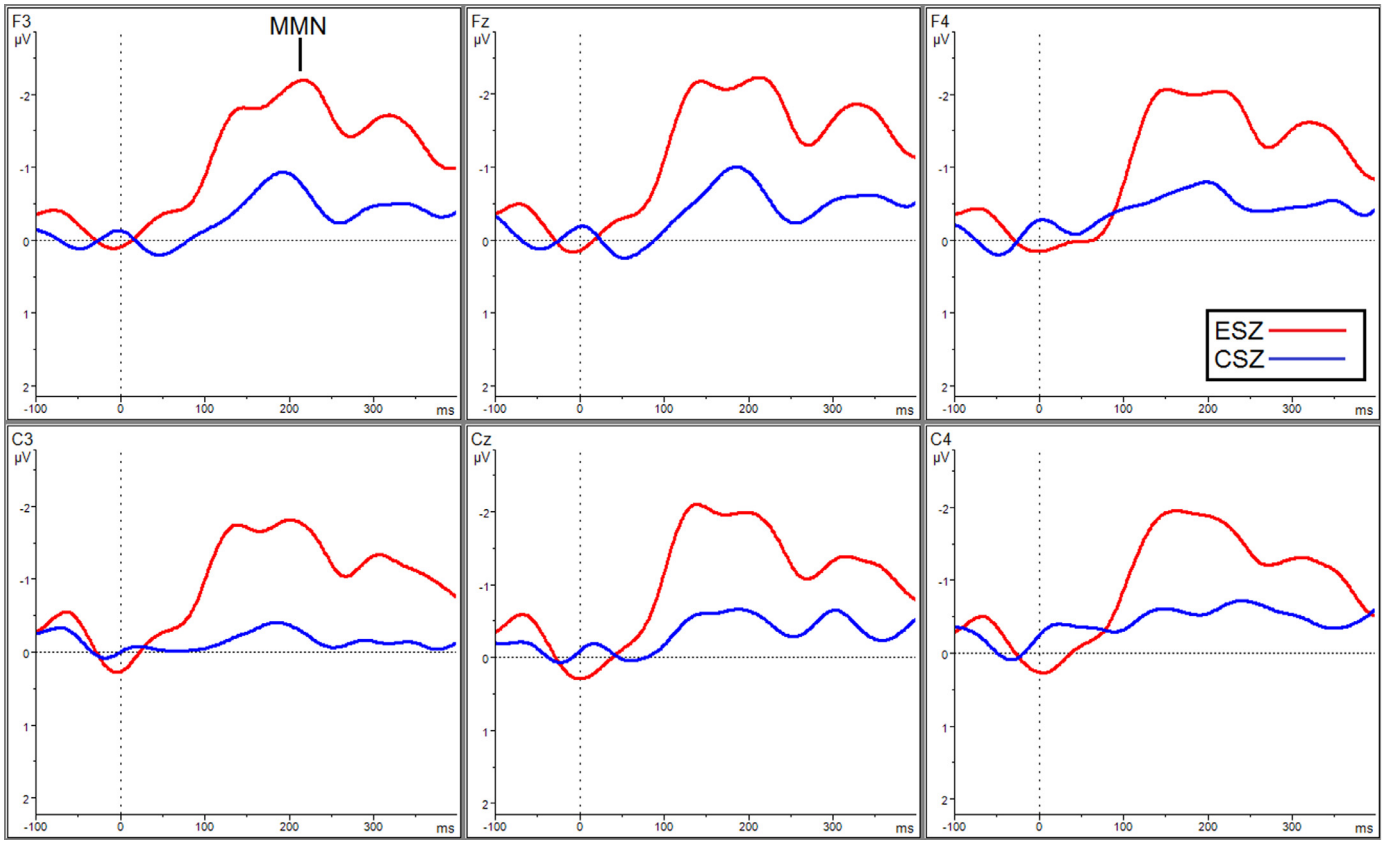

Fig. 3. Grand averaged MMN difference waves for early schizophrenia patients (ESZ) and chronic schizophrenia patients (CSZ) at frontal and central electrode sites. There was a significant difference between the groups at all sites ($p < .05$).

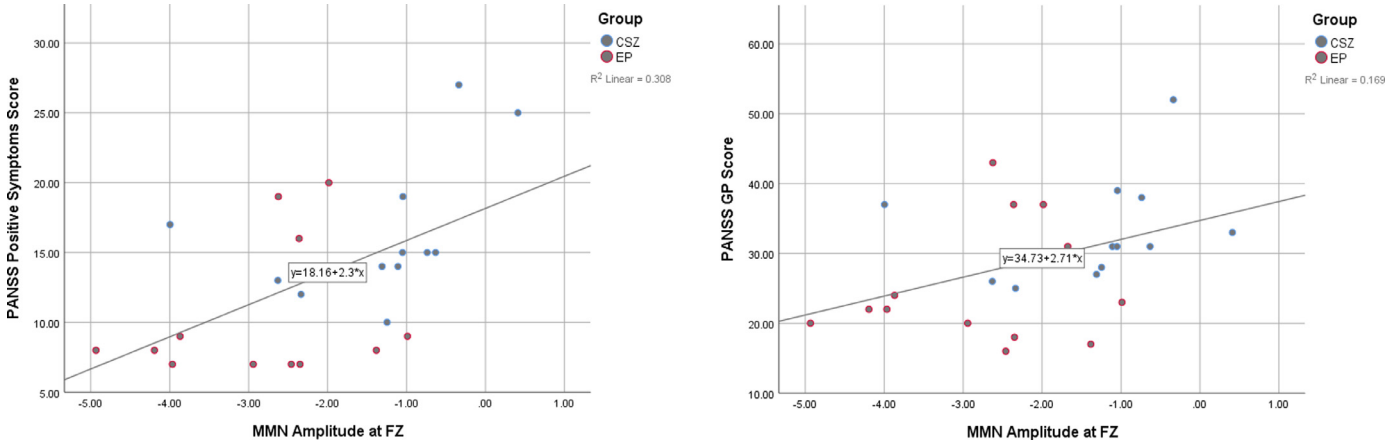

Fig. 4. Scatterplots illustrating significant correlations ($p < .05$) between MMN Amplitude at F_Z and PANSS scores on the positive and general psychopathology (GP) subscales in the combined SZ sample (i.e. ESZ + CSZ; $n = 25$).

chronic schizophrenia groups may over-represent severely ill patients who remain in treatment, while early illness groups contain a heterogeneous mix of those who will remain ill and those who will no longer need treatment (Ram et al., 1992). Additionally, longer duration of illness has been linked to less clinical improvement and poorer trajectory (Szymanski et al., 1996). Additionally, the nature of symptoms, and the processes that produce them, may change in different stages of schizophrenia (McGlashan and Fenton, 1992; Mojtabai, 1999).

There were several limitations to this study, most notably that a cross-sectional design was utilized rather than a longitudinal design. Future work should attempt to assess the same group of clinical participant at different time points in order to best characterize change over the course of the illness. Another limitation is the small sample size employed in each experiment. It must be noted, however, that while the samples are small, they are certainly not unreasonable compared to similar studies which have reported findings with samples of 10 (Ford et al., 2010), 13 (Javitt et al., 2000), and 18 (Kaur et al., 2013) SZ participants. Additionally, the *p*-value approach to significance testing, which is particularly susceptible to the effects of low power, has been supplemented with the reporting of effect sizes. While not a limitation per se, future studies may wish to directly compare native-language and foreign phonemes in early and chronic schizophrenia populations to as to investigate the influence of previous language learning on early speech sound processing.

In conclusion, we report significant reductions of mismatch negativity elicited by speech sounds in chronic schizophrenia participants, but not those within the first five years of illness (i.e. early schizophrenia). Whether these deficits progressively worsen in a linear fashion across the illness, or degrade rapidly then stabilize during a critical period early in the illness is currently unknown. Dysfunction of the early processing of speech sounds appears to have important implications regarding overall function and may be an important treatment target in this population.

CRediT authorship contribution statement

Derek J. Fisher: Conceptualization, Data curation, Writing - original draft. **Erica D. Rudolph:** Writing - original draft, Data curation. **Emma M.L. Ells:** Writing - original draft, Data curation. **Verner J. Knott:** Conceptualization, Writing - review & editing. **Alain Labelle:** Conceptualization, Writing - review & editing. **Philip G. Tibbo:** Writing - review & editing, Conceptualization.

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Disclosures

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Supplementary materials

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