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Alterations of mismatch negativity (MMN) in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness

Derek J. Fisher [a,b,c,d,*], Alain Labelle [d,e], Verner J. Knott [c,d,e]

[a] Department of Psychology, Mount Saint Vincent University, Halifax, Nova Scotia, Canada
[b] Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Department of Psychology, Carleton University, Ottawa, Ontario, Canada
[d] University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada
[e] Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

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ABSTRACT

Auditory verbal hallucinations (AHs), or hearing 'voices', are one of the hallmark symptoms of patients with schizophrenia. The primary objective of this study was to compare hallucinating schizophrenia patients with respect to differences in deviance detection, as indexed by the auditory mismatch negativity (MMN). Patients were recruited during an acute psychotic episode requiring hospitalization, during which time symptoms of psychosis, including auditory hallucinations, are likely to be at their most severe.

MMNs to duration, frequency, gap, intensity and location deviants (as elicited by the 'optimal' multi-feature paradigm) were recorded in 12 acutely ill schizophrenia patients (SZ) with persistent AHs and 15 matched healthy controls (HC). Electrical activity was recorded from 32 scalp electrodes. MMN amplitudes and latencies for each deviant were compared between groups and were correlated with trait (PSYRATS) and state measures of AH severity and Positive and Negative Syndrome Scale (PANSS) ratings in SZs.

There were significant group differences for duration, gap, intensity and location MMN amplitudes, such that SZs exhibited reduced MMNs compared to HCs. Additionally, gap MMN amplitudes were correlated with measures of hallucinatory state and frequency of AHs, while location MMN was correlated with perceived location of AHs. In summary, this study corroborates previous research reporting a robust duration MMN deficit in schizophrenia, as well as reporting gap, intensity and location MMN deficits in acutely ill schizophrenia patients with persistent AHs. Additionally, MMN amplitudes were correlated with state and trait measures of AHs. These findings offer further support to previous work suggesting that the presence of auditory hallucinations may make a significant contribution to the widely reported MMN deficits in schizophrenia.

1. Introduction

Schizophrenia (SZ) is a uniquely devastating disease, typically emerging during young adulthood with a lifetime prevalence rate of 4.0% across the globe (Saha et al., 2005). Auditory verbal hallucinations (AHs), or hearing 'voices', are one of the hallmark symptoms of patients with SZ (David, 1999); within schizophrenia patients, auditory hallucinations have a reported prevalence of 50–80% (Andreasen and Flaum, 1991). It has been suggested that AHs may drive the normal hearing apparatus (temporal cortex) and compete with external speech for limited neural resources allocated to that apparatus (Woodruff et al., 1997; Woodruff, 2004). Accordingly, the study of AHs is becoming a larger field within research into this devastating illness (Ford et al., 2012).

Within the fields of attention and information processing, the electroencephalographically (EEG)-derived event-related potentials (ERPs) provide an exquisitely sensitive method of indexing cognition with a temporal resolution far superior to some of the more sophisticated imaging techniques (i.e. PET, fMRI), making this methodology far more suitable for capturing instantaneous changes in information processes. The mismatch negativity (MMN) is an ERP that is elicited by any discriminable change in auditory stimulation irrespective of whether or not one is consciously aware of, or attending to, such a change (Näätänen, 1982, 1992); the resulting waveform is a negative peak with a frontal-topography maximum amplitude and an expected peak latency of 90–250 ms. The MMN is elicited by auditory stimuli that may deviate in any number of ways from the standard, with deviations in frequency, duration, intensity and location eliciting an MMN (Näätänen and Alho, 1997).

Given the cognitive deficits associated with schizophrenia, and the view that the MMN provides a useful index of pre-attentive cognition, research into the mismatch negativity in affected patients has been a major point of interest since the first study linking the two was published (Shelley et al., 1991). In general, chronic SZ patients exhibit robust MMN deficits (Javitt et al., 1993; Youn et al., 2002; Umbricht et al., 2003), especially to duration deviants (Michie, 2001), however

* Corresponding author at: Department of Psychology, Mount Saint Vincent University, 166 Bedford Hwy., Halifax, NS, Canada B3M 2J6. Tel.: +1 902 457 5503.
E-mail addresses: derek.fisher@msvu.ca, Derek.Fisher@rohcg.on.ca (D.J. Fisher).

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MMN reduction in SZ has been reported with frequency (Javitt et al., 1993; Hirayasu et al., 1998; Horton et al., 2010; Todd et al., 2008), intensity (Fisher et al., 2008a; Todd et al., 2008) and location (Alain et al., 2002) deviants as well. Recently, there has been an increased focus on AHs, and their contribution to illness-associated MMN deficits, in studies examining MMN in SZ (Oades et al., 1996; Hirayasu et al., 1998; Schall et al., 1999; Youn et al., 2002; Fisher et al., 2008a, 2008b, 2011b). Overall, these efforts have tended to focus on correlations between MMN amplitude and self-report measures of hallucinations with uneven results, though the three studies that did find significant correlations reported that as measures of hallucinations increase there is a corresponding decrease in MMN amplitude (Hirayasu et al., 1998; Youn et al., 2002; Fisher et al., 2011b). To date there is one study that directly compared SZ patients with clear, persistent auditory hallucinations to those with no auditory hallucinations; hallucinating patients exhibited reduced MMN amplitude to duration (vs. healthy controls and non-hallucinating patients) and intensity deviants (vs. healthy controls), while non-hallucinating patients were not significantly different than healthy controls (Fisher et al., 2008a). Taken together, these findings corroborate the suggestion that auditory hallucinations compete with incoming external stimuli for finite resources in the auditory cortex (Woodruff, 2004), resulting in reduced MMN.

The primary objective of this study was to compare hallucinating SZ patients with respect to differences in deviance detection during an acute psychotic episode requiring hospitalization, during which time symptoms of psychosis, including auditory hallucinations, are likely to be at their most severe.

Employing the multi-feature MMN paradigm proposed by Näätänen et al. (2004), it is hypothesized that during hospitalization deviant detection, as expressed by MMN, will be reduced in hallucinating patients (HP) compared to non-patient healthy controls (HC). Furthermore, it is expected that alteration of auditory change detection, as indexed by MMN amplitude, will be associated with measures of AH state and trait, such that smaller MMNs are observed in patients with more severe AH trait and during exacerbations of AH state.

2. Materials and methods

2.1. Experimental participants

Twelve patient volunteers, all presenting with a primary diagnosis of SZ, were recruited from the Inpatient Schizophrenia Clinical Unit of the Royal Ottawa Mental Health Centre (ROMHC). At the time of admission to the study, all patient volunteers were experiencing acute exacerbation of their illness, as indicated by a score on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989) between 60 and 120 (Sechter et al., 2002). Additionally, all patients had a current history of AHs, as evidenced by a score ≥ 3 ("mild or greater hallucinatory experiences") on the hallucination item of the PANSS positive symptom scale (based on physician assessment). The presence of AHs was subsequently confirmed using the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS; Haddock et al., 1999).

All patient participants were primarily right-handed, as per the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), between the ages of 18–55 and their primary medication was limited to one of the atypical anti-psychotics. All participants were able to understand spoken and written English. Due to the auditory requirements of the study, participants were required to demonstrate normal hearing according to an audiometric assessment, using a method of descending-limits.

Participants were excluded if they met any of the following criteria: co-morbid DSM-IV TR Axis I disorder; current history of drug abuse or dependence; recent (one year) history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; treatment with anxiolytics or anti-depressants; electro-convulsive therapy (ECT) treatment within the previous year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

2.2. Control participants

HCs were 15 right-handed, healthy volunteers, with negative psychiatric, medical, neurological and alcohol/drug abuse histories (by self-report), reporting non-use of medications, and displaying normal hearing. Experimental and control groups were matched with respect to age and gender. Two-tailed independent samples t-tests were used to compare group means on demographic variables. While attempts were made to match the groups for years of education this proved to be difficult as SZ patients who are more likely to require hospitalization tend to have an early age of onset (Olfson et al., 2011), which interferes with schooling. As such, there was a significant difference, $t = -3.45$, $p = .004$, between groups on years of education. Participant demographics are shown in Table 1.

2.3. Study procedure

Testing was conducted around midday (12:30 p.m.–2:30 p.m.) with participants being required to abstain from drugs, medications (except for anti-psychotics and adjunct drugs), and alcohol beginning at midnight of the previous day. For experimental participants, the test session took place as close as possible to hospital admission and before stabilization of acute exacerbation of symptoms. Following informed consent procedures, all volunteers were assessed with respect to the MMN paradigm, during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli. Rest intervals of ~1 min were inserted between each of the test blocks of the MMN paradigm. Following the MMN paradigm, hallucination state ratings (HSR) were assessed. Subjective ratings were carried out in a manner similar to that used by Margo et al. (1981), requiring participants to subjectively assess the duration, loudness and clarity of hallucinations experienced during the EEG recording.

The study was conducted following approval of both the Research Ethics Board of the Royal Ottawa Health Care Group (ROHCG) and the Carleton University Ethics Committee for Psychological Research.

2.4. Task stimuli: 5-deviant 'optimal' multi-feature MMN

This study employed the 5-deviant multi-feature MMN paradigm developed by Näätänen et al. (2004), which has been shown to have a superior signal-to-noise ratio compared to the traditional two-stimulus auditory oddball paradigm (Thonnessen et al., 2008). Presented through headphones, all stimuli (with the exception of the intensity deviants) were at a sound pressure level (SPL) of 70 dB with equal phase intensity in each channel and a stimulus-onset asynchrony of 500 ms. The stimuli were presented in 3 blocks of 5 min each (1845 stimuli) for a total of 15 min (5535 stimuli).

Table 1
Summary of participant demographics and trait questionnaires (mean ± SE).

	Patients	Controls
Age	30.60 (3.41)	31.67 (3.03)
Years of education	12.07 (0.92)	16.07 (0.69)
PSYRATS	25.22 (3.26)	–
PANSS positive symptom	19.43 (1.59)	–
PANSS negative symptom	19.71 (1.48)	
PANSS hallucination item	3.57 (0.57)	–
PANSS general psychopathology	35.29 (1.01)	–
HSR-duration	2.73 (0.62)	
HSR-loudness	2.82 (0.54)	
HSR-clarity	3.45 (0.82)	