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Equivalent mismatch negativity deficits across deviant types in early illness schizophrenia-spectrum patients

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ABSTRACT

Neurophysiological abnormalities in auditory deviance processing, as reflected by the mismatch negativity (MMN), have been observed across the course of schizophrenia. Studies in early schizophrenia patients have typically shown varying degrees of MMN amplitude reduction for different deviant types, suggesting that different auditory deviants are uniquely processed and may be differentially affected by duration of illness. To explore this further, we examined the MMN response to 4 auditory deviants (duration, frequency, duration + frequency "double deviant", and intensity) in 24 schizophrenia-spectrum patients early in the illness (ESZ) and 21 healthy controls. ESZ showed significantly reduced MMN relative to healthy controls for all deviant types ($p < 0.05$), with no significant interaction with deviant type. No correlations with clinical symptoms were present (all $ps > 0.05$). These findings support the conclusion that neurophysiological mechanisms underlying processing of auditory deviants are compromised early in illness, and these deficiencies are not specific to the type of deviant presented.

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1. Introduction

Auditory mismatch negativity (MMN) is an event-related potential (ERP) component elicited by an infrequent deviant sound presented within a series of repeated standard sounds (Naatanen, Teder, Alho, & Lavikainen, 1992). MMN is considered to be an index of sensory "echoic" memory, since the detection of auditory deviance depends on the short-term formation of a memory trace of the standard sounds present in the immediately preceding time window (Naatanen, 2000; Naatanen, Jacobsen, & Winkler, 2005). Recent interpretations of the MMN have emphasized its reflection of both short-term (seconds) and longer term (minutes to hours) synaptic plasticity in the service of auditory sensory/perceptual learning, since the amplitude of the MMN to a deviant stimulus increases as a function of the number of repetitions of the preceding standard stimulus (Stephan, Baldeweg, & Friston, 2006). From this perspective, memory traces of the recent auditory past code predictions of future auditory events, with the MMN signaling a prediction

error when the auditory expectancy is violated by a deviant stimulus (Friston, 2005; Garrido, Kilner, Stephan, & Friston, 2009; Todd, Michie, Schall, Ward, & Catts, 2012). MMN can be elicited by deviance in one or more dimensions of auditory stimuli, including pitch, duration, intensity and location (Naatanen, Pakarinen, Rinne, & Takegata, 2004), as well as in response to deviance in more complex auditory patterns (Paavilainen, Simola, Jaramillo, Naatanen, & Winkler, 2001a; Saarinen, Paavilainen, Schoger, Tervaniemi, & Naatanen, 1992; Tervaniemi, Maury, & Naatanen, 1994; van Zuijen, Sussman, Winkler, Naatanen, & Tervaniemi, 2004). MMN elicited by different types of auditory deviance arise from at least partially distinct neuronal populations in the cortex (Alho, 1995; Csepe, 1995; Deouell, Bentin, & Giard, 1998; Giard, Perrin, Pernier, & Bouchet, 1990; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005; Paavilainen, Alho, Reinikainen, Sams, & Naatanen, 1991), suggesting that MMN should be thought of as a family of related ERP components arising from largely non-overlapping neural sources (Naatanen, Paavilainen, Rinne, & Alho, 2007). Importantly, MMN is elicited pre-attentively (Fischer et al., 1999; Naatanen & Alho, 1995; Naatanen et al., 1992), allowing an assessment of auditory processing deficits in neuropsychiatric disorders without the confounding influences of motivation and attention associated with higher order cognitive tasks (Mathalon & Ford, 2008).

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MMN amplitude reduction in schizophrenia is well-documented (Naatanen & Kahkonen, 2009; Nagai et al., 2013a; Umbricht & Krljes, 2005), including in chronic (Brockhaus-Dumke et al., 2005; Catts et al., 1995; Jahshan et al., 2012; Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Javitt, Grochowski, Shelley, & Ritter, 1998; Javitt, Shelley, Silipo, & Lieberman, 2000b; Kiang, Braff, Sprock, & Light, 2009; Light & Braff, 2005; Magno et al., 2008; Michie et al., 2000; Oades et al., 2006; Oknina et al., 2005; Rasser et al., 2011; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Shelley et al., 1991; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006), recent onset (Atkinson, Michie, & Schall, 2012; Jahshan et al., 2012; Javitt et al., 2000b; Kaur et al., 2011, 2012b, 2013, Perez et al., 2014; Todd et al., 2008; Umbricht et al., 2006), and some (Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Catts et al., 1995) but not all (Devrim-Ucok, Keskin-Ergen, & Ucok, 2008; Kirino & Inoue, 1999; Korostenskaja et al., 2005) unmedicated patients. The status of MMN in first episode schizophrenia is more controversial, with some studies reporting reduced frequency-deviant MMN (Oknina et al., 2005) or duration-deviant MMN (Bodatsch et al., 2011; Hermens et al., 2010; Kaur et al., 2011; Nagai et al., 2013b; Oades et al., 2006), at least in patients lacking any college education (Umbricht et al., 2006), but other studies reporting normal duration-deviant MMN (Magno et al., 2008) or frequency-deviant MMN (Bodatsch et al., 2011; Devrim-Ucok et al., 2008; Magno et al., 2008; Nagai et al., 2013b; Salisbury et al., 2002; Valkonen-Korhonen et al., 2003). In addition, several longitudinal studies of first episode patients have documented progressive reduction of MMN amplitude over 2.5 months (Devrim-Ucok et al., 2008), 1 to 2.5 years (Kaur et al., 2013), or 1.5 years (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007), with one report showing this reduction to be associated with volume decline in left Heschel's gyrus (Salisbury et al., 2007). Importantly, MMN deficits are also seen in people at clinical high risk for schizophrenia (for review, see Nagai et al., 2013a), with greater deficits seen in those who later convert to psychosis (Bodatsch et al., 2011; Perez et al., 2014; Shaikh et al., 2012) and in adolescents with psychotic experiences (Murphy et al., 2013).

Despite the general convergence of research findings showing MMN amplitude reduction in schizophrenia, there is also significant variability among studies (Umbricht & Krljes, 2005). This variability may be driven, at least in part, by differences in the types of deviant stimuli used to elicit MMN, since it appears that distinct neural populations process different dimensions of auditory deviance (Alho, 1995; Csepe, 1995; Deouell et al., 1998; Giard et al., 1990; Molholm et al., 2005; Paavilainen et al., 1991). To date, substantial evidence suggests that duration-deviant MMN is more sensitive to schizophrenia than frequency-deviant MMN (Michie et al., 2000; Todd et al., 2008; Umbricht & Krljes, 2005). Some evidence suggests that duration-deviant MMN deficits may be evident early in the disorder (Bodatsch et al., 2011; Shaikh et al., 2012), while frequency MMN deficits may emerge later as a marker of illness progression (Naatanen & Kahkonen, 2009; Nagai et al., 2013a). Nonetheless, frequency-deviant MMN deficits have been reported in schizophrenia across the illness course (Salisbury et al., 2007; Umbricht & Krljes, 2005; Umbricht et al., 2006), including the prodromal period preceding psychosis onset (Perez et al., 2014).

Although speculative, inconsistency across studies may be due to differences in composition of the samples, with one sample being more sensitive to duration deviants and another being more sensitive to frequency deviants. One approach to overcoming this is to combine deviance features such as duration and frequency within a single stimulus, potentially facilitating detection of MMN deficits regardless of which MMN type is more deficient in a given patient (e.g., (Perez et al., 2014)). Prior studies (Levanen, Hari, McEvoy, & Sams, 1993; Paavilainen, Valppu, & Naatanen, 2001b; Schroger, 1995; Takegata, Paavilainen, Naatanen, & Winkler, 1999; Wolff & Schroger, 2001) have shown that when two features of a stimulus are deviant ("double-deviant" stimulus), the deviant features are processed in parallel, with MMN showing additive (Paavilainen et al., 2001b; Takegata et al., 1999) or at least enhanced (Schroger, 1995; Wolff & Schroger, 2001) amplitude relative to the amplitudes of corresponding single-deviant MMNs. Observing a significant MMN reduction in schizophrenia patients becomes more likely when the stimulus elicits a larger MMN (Javitt et al., 1998), further positioning double-deviant MMNs to be more sensitive to illness pathophysiology than single deviant MMNs.

While potentially increasing sensitivity to disease effects, the use of double-deviant stimuli does not allow direct comparisons of MMNs elicited by different types of auditory deviance. Indeed, much of the research on MMN deficits in schizophrenia has employed paradigms using only one or two types of auditory deviance (Umbricht & Krljes, 2005), providing limited opportunities to directly compare the sensitivities of different types of MMN illness effects. To overcome this limitation, multi-deviant paradigms, in which two or more types of deviant stimuli are presented along with standard stimuli within a single sequence, have been developed and validated (Naatanen et al., 2004). In a previous application of such a multi-deviant MMN paradigm to schizophrenia, Todd and colleagues (Todd et al., 2008) found robust deficits in duration- and intensity-deviant MMN, but normal frequency-deviant MMN, in schizophrenia patients early in their illness. In contrast, chronic schizophrenia patients showed the greatest MMN amplitude reduction to frequency deviants, along with a smaller reduction in duration-deviant MMN and normal intensity-deviant MMN. Subsequent studies that applied a multi-deviant paradigm to chronic schizophrenia patients found equivalently reduced MMN amplitudes across deviant types including duration-, intensity-, and frequency-deviants (Friedman, Sehatpour, Dias, Perrin, & Javitt, 2012; Todd et al., 2014).

In order to examine the sensitivity of different types of MMN, including double-deviant stimuli, to the effects of psychosis relatively early in the illness course, we assessed MMN using a multi-deviant paradigm in a sample of people diagnosed with a schizophrenia-spectrum illness within 5 years of treatment initiation and an age-matched healthy control sample. The paradigm, which was an adaptation of the "Optimum 1" paradigm developed for clinical research studies (Naatanen et al., 2004), included an intensity-deviant, duration-deviant, frequency-deviant, and double-deviant (duration + frequency) auditory stimuli. We hypothesized that MMN would be reduced in these patients compared to healthy controls, and that the size of this reduction would significantly depend on the type of auditory deviance. Among deviant types, we predicted that the double deviant-MMN would show greater reduction than any single deviant MMN type, and that the duration and intensity single deviants would result in greater MMN reduction than the frequency deviant, based on the literature (Todd et al., 2008).

2. Method

2.1. Participants

Study participants included 24 patients on the schizophrenia spectrum early in their illness (ESZ), defined as being within 5 years of first hospitalization or initiation of treatment, and 21 age-matched healthy control (HC) subjects. Among the ESZ group, two patients also met criteria for an anxiety disorder (Panic Disorder, Generalized Anxiety Disorder and Obsessive-Compulsive Disorder). All but four ESZ patients were taking anti-psychotic medication (see Table 1), which were converted to chlorpromazine equivalents for further analysis (Leucht et al., 2014). In addition,

Table 1
Group demographic data.

Measure (group difference *p*-value)	ESZ *N* = 24		HC *N* = 21	
	N	%	N	%
Gender (*p* = 0.34)				
Female	5	20.8	7	33.3
Male	19	79.2	14	66.7
Handedness[a] (*p* = 0.09)				
Right	19	79.2	21	100
Left	4	16.7	0	0
Ambidextrous	1	4.2	0	0
Diagnostic subtype				
Paranoid	9	37.5		
Disorganized	1	4.2		
Undifferentiated	5	20.8		
Residual	1	4.2		
Schizoaffective	6	25		
Psychosis not otherwise specified	2	8.3		
Antipsychotic type				
Atypical alone	19	79.2		
Typical alone	0	0		
Both	1	4.2		
None	4	16.7		
	M	SD	M	SD
Age, years (*p* = 0.46)	23.95	5.17	22.89	4.26
Education, years[†] (*p* = 0.02)	13	2.43	14.81	2.71
Parental SES[b,†] (*p* = 0.01)	42.46	16.67	30.48	13.71
Duration of illness, years	1.39	1.37		
CPZ 100 mg/d equivalents[c]	3.71	6.73		
PANSS symptom scores[d]				
Positive (mean of 7 items)	2.21	0.56		
Negative (mean of 7 items)	2.4	0.67		
General (mean of 16 items)	2.02	0.39		

Note. Numbers and percentages of participants are reported for gender, handedness, diagnostic subtype, and antipsychotic type. Group means (M) and standard deviations (SD) are reported for age, average parental socioeconomic status (SES), duration of illness, and mean Positive and Negative Syndrome Scale (PANSS) ratings. Gender and handedness were analyzed with Pearson chi-square tests. Age and parental socioeconomic status were analyzed with independent samples *t*-tests. ESZ = early illness schizophrenia patients, HC = healthy controls.

[a] The Crovitz and Zener (1962) questionnaire was used to measure handedness.

[b] The Hollingshead (1975) four-factor index of parental socioeconomic status is based on a composite of maternal education, paternal education, maternal occupational status, and paternal occupational status. Lower values signify higher socioeconomic status.

[c] Chlorpromazine (CPZ) dose equivalents in 100 milligram per day (mg/d) calculated based on Leucht et al. (2014). Medication dosages were unavailable for 2 patients. 4 patients were not taking any medication.

[d] PANSS ratings were collected from 23 early illness schizophrenia patients. The mean PANSS score for items in each category is reported for positive (mean of 7 items), negative (mean of 7 items), and general (mean of 16 items) symptoms.

[†] *p* < 0.05, two-tailed.

3 patients were taking anti-depressants (venlafaxine, citalopram, sertraline), 5 patients were taking benzodiazepines (3× lorazepam and 2× clonazepam), 1 patient was taking a beta-blocker (propranolol), 3 patients were taking anti-Parkinsonian medication (benztropine), and 1 patient was taking a mood stabilizer (lithium).

ESZ patients were referred to the study through the Specialized Treatment Early in Psychosis (STEP) program at Yale University and other community providers. HC were recruited through advertisements and word of mouth. Exclusion criteria for both groups included a history of illicit substance dependence or substance abuse within the past year, a history of significant medical or neurological illness, or a history of head injury resulting in loss of consciousness. HC participants were also excluded if they met criteria for a current or past Axis I mood or psychotic disorder or if they had a first degree relative with a history of an Axis I psychotic disorder (including bipolar I disorder). Both groups were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al.,

1997), and all study interviews were administered by a trained research assistant, psychiatrist, or clinical psychologist.

This study was approved by the institutional review board at Yale University. All adult participants provided written informed consent. In the case of a minor participant, written informed assent was obtained, along with written informed consent from a parent. Clinical and demographic data for all participants are presented in Table 1.

2.2. Clinical ratings

Symptoms were rated by trained clinical staff using the Positive and Negative Syndrome Scale (PANSS; (Kay, Fiszbein, & Opler, 1987)). Ratings were available for all but one patient and were obtained within 16 days of ERP assessment (mean ± SD = 5.87 ± 5.13 days).

2.3. MMN paradigm

MMNs were assessed using a multi-deviant paradigm modeled after the "Optimum-1" paradigm (Naatanen et al., 2004). In our adaptation of this paradigm, four types of auditory deviants were presented within the same stimulus sequence (each with probability [*p*] = 0.125): duration, frequency, double-deviant (frequency + duration), and intensity. Every other stimulus in the sequence was a standard tone (*p* = 0.5), and each remaining stimulus was one of the four deviant tones presented in pseudorandom order. Standard tones had 5 ms rise and fall times, lasted 75 ms, and comprised 3 sinusoidal partial frequencies of 500, 1000, and 1500 Hz. These partials were presented at 75 dB SPL, 72 dB SPL, and 69 dB SPL, respectively. Deviant tones were identical to the standard tone except for a specified deviant feature. Duration-deviants were presented for 125 ms, which was 50 ms longer than the standard tone. Half of the frequency deviants had sinusoidal partials 10% higher than standard tones and half were 10% lower. Double-deviants were presented for 125 ms, and half were higher in frequency and half were lower (using same parameters as frequency-deviants). Half of the intensity-deviants were 10 dB higher than standard tones and half were 10 dB lower. Tones were presented with a 500 ms stimulus onset asynchrony. A total of 2460 tones were presented over 4 separate blocks lasting approximately 5 min each using Etymotic ER-3A insert. In an effort to minimize the influence of attention on the MMN measurements, participants were instructed to ignore auditory stimuli while performing a computerized picture-word matching task presented on a video display that required a button press response on each trial (for task details, see Perez et al., 2012).

2.4. Electroencephalographic data acquisition and preprocessing

Electroencephalographic (EEG) data were acquired using a high-impedance BioSemi Active Two recording system and a 64-channel electrode cap (Biosemi, Amsterdam, Netherlands). Continuous EEG data digitized at a rate of 1024 Hz, referenced offline to averaged earlobe electrodes, high-pass filtered at 0.1 Hz, and segmented into 1000 ms epochs time-locked to the onsets of the various types of auditory stimuli (−500 to 500 ms). Electro-oculogram (EOG) data were recorded from electrodes placed above and below the left eye and at the outer canthi of both eyes to capture vertical (VEOG) and horizontal (HEOG) eye movements. VEOG and HEOG channels were then used to correct the EEG for artifacts associated with blinks and eye movement using a regression-based algorithm (Gratton, Coles, & Donchin, 1983). Following baseline correction (−50 to 0 ms) of each EEG epoch, electrodes containing epochs with outlier values were replaced by interpolated values based on a routine implemented in a previously published automated EEG data cleaning

Table 2
Number of trials in event-related potential averages.

Stimulus type	HC		ESZ	
	M	SD	M	SD
Frequency-deviant	256.6	22.4	252.9	37.2
Frequency + duration double-deviant	260.2	17.5	251.4	37.2
Duration-deviant	262.7	18.1	250.2	37.7
Intensity-deviant	263.1	19.4	253.2	42.4
Standard	1085.8	84	1066.6	163

Note. HC = healthy controls, ESZ = early illness schizophrenia patients, M = mean, SD = standard deviation.

algorithm (Nolan, Whelan, & Reilly, 2010). Specifically, a spherical spline interpolation was applied to any channel and epoch determined to be a statistical outlier ($|z| > 3$) on one or more of four parameters, including variance (to detect additive noise), median gradient (to detect high-frequency activity), amplitude range (to detect pop-offs), and deviation of the mean amplitude from the common average (to detect electrical drift) (Delorme & Makeig, 2004). Subsequently, epochs were rejected if they contained amplitudes greater than $\pm 75\,\mu V$ in any of the electrodes included in the analysis: F3, Fz, F4, C3, Cz, C4. In the next step, ERP averages for all stimulus types were determined using a sorted averaging method shown to reduce noise in the MMN waveform by averaging over the subset of trials that optimizes the estimated signal to noise ratio (eSNR) (Perez et al., 2014; Rahne, von Specht, & Muhler, 2008) for each subject. Briefly, single-epoch root mean squared (RMS) amplitude values for each trial are calculated and sorted in ascending order for each stimulus type. The subset of sorted trials selected for ERP averaging are associated with the largest eSNR, which is the ratio of the number of trials to the variance of the amplitude values across trials. The number of trials contributing to ERPs for each stimulus type did not differ between groups (Table 2). Following sorted averaging, ERPs for all stimulus types were low-pass filtered at 30 Hz, and then standard tone ERP waves were subtracted from deviant tone ERP waves to derive difference waves. The MMNs were then identified in each subject's difference waves as the most negative peak between 160 and 290 ms for duration-deviant stimuli, and between 90 and 290 ms for the remaining deviant types. The selection of a later, 160 ms starting latency for the duration-deviant MMN search window was to avoid selecting the first peak in the grand average, which was too early in its latency to represent the long duration-deviant MMN. MMN amplitudes were quantified as the mean microvolt value within a ± 10 ms time window surrounding each MMN peak (Picton et al., 2000). MMN peak latencies were also saved for further analysis.

2.5. Statistical analysis

Group differences in MMN amplitude and latency were assessed using 4-way repeated measures analyses of variance (ANOVA) models with a between-subjects factor of group (ESZ, HC), and within-subjects factors of deviant type (duration, frequency, double, intensity), anterior/posterior lead (frontal, central), and lateral lead (left, midline, right). Greenhouse-Geisser non-sphericity correction was applied to within-subjects effects with more than two levels.

MMN amplitudes averaged over the six fronto-central electrodes (F3, Fz, F4, C3, Cz, C4) were used in correlational analyses. Spearman rank-order correlations were used to assess the relationships between MMN amplitude and PANSS Positive, Negative, and General Symptom subscale scores and chlorpromazine equivalents. Alpha was set to $p = 0.05$, two-tailed for all statistical tests.

Table 3
Analysis of variance (ANOVA) of mismatch negativity (MMN) amplitude.

MMN amplitude		
Effect	F	p-Value
Group	5.54	0.02
Deviant type	12.57	<0.001
(duration = frequency > intensity > double-deviant)		
Deviant type × group	0.13	0.95
Anterior/posterior lead (central > frontal)	20.44	<0.001
Anterior/posterior × group	0.04	0.85
Lateral lead (left > midline = right)	9.81	0.001
Lateral × group	0.36	0.65
Deviant type × anterior/posterior	3.30	0.02
Anterior/posterior (duration) (central > frontal)	4.69	0.04
Anterior/posterior (frequency) (central > frontal)	19.32	<0.001
Anterior/posterior (intensity) (central > frontal)	21.92	<0.001
Anterior/posterior (double-deviant) (central > frontal)	12.36	0.001
Deviant type × anterior/posterior × group	1.14	0.33
Deviant type × lateral	2.58	0.03
Lateral (duration) (left > midline = right)	10.78	<0.001
Lateral (frequency)	2.62	0.10
Lateral (intensity) (left > midline = right)	5.65	0.006
Lateral (double-deviant) (left > right)	4.95	0.01
Deviant type × lateral × group	0.92	0.47
Anterior/posterior × lateral	4.76	0.02
Anterior/posterior (left lead) (C3 > F3)	11.46	0.00
Anterior/posterior (midline lead) (Cz > Fz)	18.76	<0.001
Anterior/posterior (right sites) (C4 > F4)	29.17	<0.001
Anterior/posterior × lateral × group	0.98	0.37
Deviant type × anterior/posterior × lateral	1.33	0.26
Deviant type × anterior/posterior × lateral × group	1.07	0.37

Note: Larger MMN is more negative, or smaller absolute voltage.

3. Results

3.1. Demographic differences between groups

Demographic data and analyses are shown in Table 1. The groups did not significantly differ on handedness (Crovitz & Zener, 1962), gender, or age. The ESZ group had significantly lower parental socioeconomic status (SES; (Hollingshead, 1975)) than the HC group ($t = -2.609$, $p = 0.012$), as well as significantly fewer years of education ($t = 2.360$, $p = 0.023$). To account for potential confounds related to group differences in parental SES and education, group effects on MMN were also assessed using ANCOVA models with each of these variables specified as a covariate.

3.2. Group differences in MMN

Grand average ERP difference waves and scalp topography maps for all deviant types are presented in Figure 1. These plots show reduced MMN amplitude across deviant types in ESZ patients relative to HC participants. A repeated measures ANOVA of MMN amplitude revealed a significant main effect of group that did not significantly interact with deviant type, lateral lead, anterior/posterior lead, or their higher order combinations (see Table 3). Main effects of deviant type, lateral lead, and anterior/posterior lead on MMN amplitude were also present and are presented in Table 3 along with the follow-up tests conducted to parse these effects. Mean MMN amplitudes are presented in Table 4. An ANOVA on MMN latencies showed no significant main effect of group ($p = 0.894$) or interactions involving the group effect (see Table 5). Additionally, there was a main effect of deviant type that did not interact with anterior/posterior lead or lateral lead, indicating that MMN latency was longest for duration- and intensity-deviants, intermediate for frequency-deviants, and shortest for double-deviants. The pattern of main effects and interactions involving the group factor was unchanged when analyses were
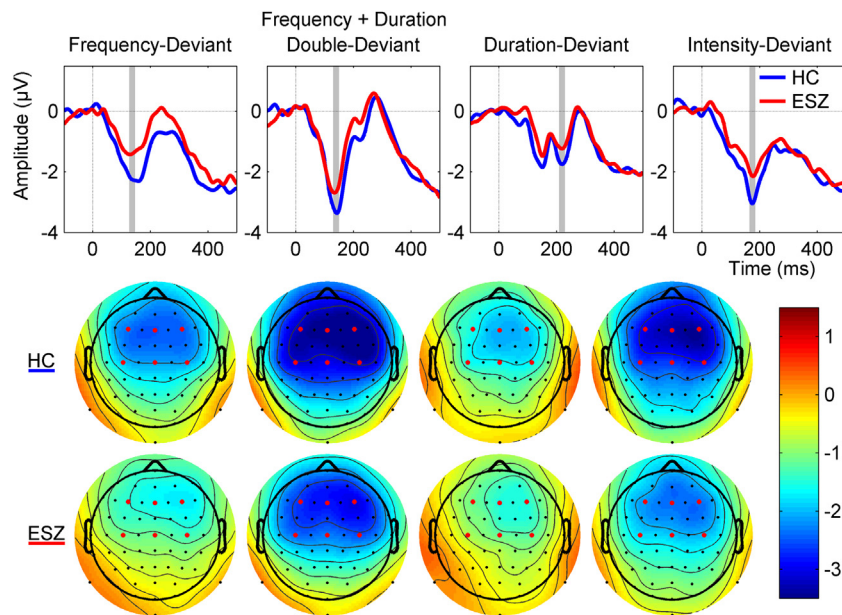
Figure 1. Mismatch negativity (MMN) for each group and deviant type. Ear-referenced event-related potential (ERP) difference waveforms averaged at Fz for frequency-deviant, frequency + duration double-deviant, duration-deviant, and intensity-deviant MMN are given for each group (top). Healthy controls (HC) are shown in blue and early illness schizophrenia patients (ESZ) in red. Scalp voltage topography maps of MMN amplitudes are shown for HC (middle) and ESZ (bottom) for each deviant type. MMN topography maps show the group means of MMN amplitudes around the peak latency ±10 ms (indicated by gray bars in ERP difference waveform plots). MMN is reduced in ESZ relative to HC across deviant types.

Table 4
Group mean and standard deviation (SD) mismatch negativity (MMN) amplitude values in microvolts for each deviant type at the six fronto-central electrode sites (F3, Fz, F4, C3, Cz, C4).

Group	Site	Duration-deviant		Frequency-deviant		Double-deviant		Intensity-deviant	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Healthy controls (N = 21)	F3	−2.52	1.03	−2.99	1.28	−3.57	1.62	−3.36	1.49
	Fz	−2.98	1.11	−3.13	1.23	−3.86	1.62	−3.63	1.69
	F4	−2.84	1.08	−3.07	1.37	−4.05	1.69	−3.71	1.79
	C3	−2.54	1.24	−2.56	1.21	−3.52	1.74	−3.00	1.46
	Cz	−2.66	1.23	−2.63	1.22	−3.43	1.69	−3.05	1.59
	C4	−2.53	1.00	−2.54	1.14	−3.55	1.65	−3.20	1.59
Early illness schizophrenia patients (N = 24)	F3	−1.96	0.98	−2.08	1.09	−3.04	1.17	−2.68	1.18
	Fz	−2.38	1.22	−2.33	1.02	−3.28	1.35	−2.92	1.13
	F4	−2.33	1.35	−2.33	0.89	−3.41	1.24	−2.90	1.02
	C3	−1.79	0.93	−1.82	1.17	−2.72	1.26	−2.30	1.22
	Cz	−2.25	1.12	−1.93	1.08	−2.69	1.39	−2.60	1.26
	C4	−2.15	0.88	−1.96	0.84	−2.83	1.09	−2.45	0.93

Table 5
Analysis of variance (ANOVA) of mismatch negativity (MMN) latency.

MMN latency		
Effect	F	p-Value
Group	0.039	0.844
Deviant type	27.03	<0.001
(duration = intensity > frequency > double-deviant)		
Deviant type × group	0.146	0.915
Anterior/posterior lead	1.11	0.298
Anterior/posterior × group	1.033	0.315
Lateral lead	1.196	0.305
Lateral × group	0.173	0.822
Deviant type × anterior/posterior	1.156	0.327
Deviant type × anterior/posterior × group	1.455	0.234
Deviant type × lateral	0.472	0.767
Deviant type × lateral × group	0.464	0.773
Anterior/posterior × lateral	0.287	0.749
Anterior/posterior × lateral × group	1.701	0.191
Deviant type × anterior/posterior × lateral	0.158	0.967
Deviant type × anterior/posterior × lateral × group	0.751	0.570

repeated using ANCOVA models with parental SES or education as covariates.

3.3. Clinical ratings correlations with MMN

There were no significant correlations between PANSS Positive, Negative, and General symptom subscale means, or antipsychotic doses in chlorpromazine equivalents, and MMN for any deviant type.

4. Discussion

We compared the MMNs elicited by four types of auditory deviance (duration, frequency, frequency + duration double-deviant, and intensity) in ESZ patients and healthy controls and found reduced MMN amplitudes in the patients regardless of deviant type. This is consistent with previous studies of recent onset schizophrenia (Atkinson et al., 2012; Higuchi et al., 2013; Jahshan et al., 2012; Javitt et al., 2000b; Oades et al., 2006; Perez

et al., 2014; Todd et al., 2008; Umbricht et al., 2006), providing further evidence that auditory deviance processing is abnormal early in the illness course. Our results are consistent with other recent onset schizophrenia studies showing reduced MMN in response to long duration (Higuchi et al., 2013; Jahshan et al., 2012; Javitt et al., 2000b; Perez et al., 2014; Todd et al., 2008; Umbricht et al., 2006), frequency (Devrim-Ucok et al., 2008; Javitt et al., 2000b; Perez et al., 2014; Salisbury et al., 2007; Umbricht et al., 2006), frequency + duration combination (Perez et al., 2014), and intensity (Todd et al., 2008) auditory deviants. However, our results are inconsistent with some studies showing normal frequency-deviant MMN in recent onset (Todd et al., 2008) or first episode samples (Devrim-Ucok et al., 2008; Magno et al., 2008; Mondragon-Maya et al., 2013; Salisbury et al., 2002; Valkonen-Korhonen et al., 2003).

While confirming a reduction in MMN in ESZ, our results failed to support the hypothesis that the degree of MMN deficit observed significantly depends on the type of auditory deviance used to elicit the MMN. This conflicts with a report of recent onset patients having reduced duration and intensity MMN, but normal frequency MMN (Todd et al., 2008). It is possible that paradigm differences contributed to these conflicting results, as our MMN paradigm included a double-deviant, whereas the earlier report did not (Todd et al., 2008). While it is also possible that our study was not sufficiently powered to detect a significant group x deviant type interaction, it should be noted that our recent onset sample was larger than the sample in the earlier report (Todd et al., 2008). Moreover, of the few studies that directly compared different deviant types, several failed to support significant dependence of the MMN deficit on the type of MMN assessed in recent onset (Javitt et al., 2000b; Perez et al., 2014; Umbricht et al., 2006) and chronic patients (Friedman et al., 2012; Todd et al., 2014). Thus, despite the view that has emerged from the larger schizophrenia literature (Michie et al., 2000; Naatanen & Kahkonen, 2009; Umbricht & Krljes, 2005) that long duration MMN is more sensitive to schizophrenia than other types of MMN, particularly during the earlier phases of the illness (Bodatsch et al., 2011; Nagai et al., 2013a, 2013b), this view has not been consistently supported by studies that directly compare subtypes of MMN in early schizophrenia patients (Javitt et al., 2000b; Perez et al., 2014; Umbricht et al., 2006).

Because we saw MMN reductions to both frequency and duration deviants, it follows that a reduction in the frequency + duration double-deviant would also be evident. This was true, and although combining two features of auditory deviance did not produce fully additive effects on MMN amplitude (Paavilainen et al., 2001b; Takegata et al., 1999), the double deviant MMNs were somewhat larger than the corresponding single deviant MMNs and were otherwise similar in morphology to waveforms seen in previous studies of double deviants (Levanen et al., 1993; Wolff & Schroger, 2001). Nonetheless, our results did not support our hypothesis that the frequency + duration double-deviant MMN would be more sensitive to ESZ than the corresponding single-deviant MMNs. In a previous study of patients at clinical high risk for psychosis (Perez et al., 2014), we found a similar deficit that was comparable in magnitude for the frequency + duration double-deviant MMN and the two corresponding single deviant MMNs, particularly in those who subsequently converted to psychosis. However, in that study, the double-deviant MMN was a significantly stronger predictor of time to psychosis onset than either of the single-deviant MMNs, suggesting that the double-deviant MMN may have advantages for predicting the course of psychosis but not for capturing a larger MMN deficit at a single cross-section of time.

While intensity-deviant MMN has not been studied as often as frequency- and duration-deviant MMN in schizophrenia, our results corroborate prior findings of reduced intensity-deviant MMN in recent onset (Todd et al., 2008) and in chronic schizophrenia (Fisher, Labelle, & Knott, 2008; Fisher, Labelle, & Knott, 2012). The similarity of the schizophrenia deficits in intensity- and long-duration deviant MMNs in our study and in the Todd et al. (2008) study raises the interesting question as to whether these are really distinct forms of MMN. According to Bloch's Law from auditory psychophysics, longer duration auditory stimuli are perceived as more intense due to the effects of temporal integration (Stevens & Hall, 1966). Thus, long duration-deviant auditory stimuli are likely to engage the generators of both duration- and intensity-deviant MMN, as has been previously noted (Michie et al., 2000; Todd et al., 2008). Accordingly, it remains unclear whether the frequently replicated schizophrenia deficit in long-duration deviant MMN reflects deficient processing of duration deviance or intensity deviance.

Unlike previous studies in recent onset patients (Devrim-Ucok et al., 2008; Magno et al., 2008; Mondragon-Maya et al., 2013; Salisbury et al., 2002; Valkonen-Korhonen et al., 2003), we found reduced amplitude MMN to frequency deviants, perhaps due to differences in duration of illness between studies. Analysis of 10 studies in schizophrenia patients (Umbricht & Krljes, 2005) found that duration of illness was positively correlated with observed effect sizes for frequency deviant MMN, indicating that patients with longer duration illness have smaller MMN to frequency deviants. Moreover, a recent multi-deviant (frequency, duration, intensity, glide type) MMN study of chronic schizophrenia patients by Todd et al. (2014) replicated the MMN amplitude deficit but did not find significant dependence of the deficit on deviance type. In the present sample, duration of illness ranged from 0 to 5 years with the majority of subjects falling within 3 years of diagnosis. A number of studies finding no deficits looked primarily at the time of first hospitalization for psychosis (Devrim-Ucok et al., 2008; Mondragon-Maya et al., 2013; Salisbury et al., 2002; Valkonen-Korhonen et al., 2003), or within 3 months of first diagnosis (Magno et al., 2008), although one study (Todd et al., 2008) examining patients within 5 years of diagnosis also found no frequency MMN reduction. Consistent with the present results, a study of patients within 3 years of diagnosis found nearly significant ($p = 0.06$) MMN reduction for frequency deviants (Javitt et al., 2000b). Additionally, a longitudinal study assessing MMN at first hospitalization with a 1.5-year follow-up showed no deficits initially, but showed frequency MMN reductions at follow-up (Salisbury et al., 2007), suggesting that frequency MMN deficits are not evident immediately after illness onset, but become evident soon after. However, this view is challenged by recently published data from our group showing deficits in frequency-deviant MMN to be present in clinical high risk patients, particularly those who subsequently convert to psychosis (Perez et al., 2014).

No correlations between MMN amplitude and symptom ratings were present, which is consistent with a number of previous studies in schizophrenia patients (Umbricht & Krljes, 2005), but not other studies showing relationships with negative symptoms (Catts et al., 1995; Javitt, Shelley, & Ritter, 2000a; Kasai et al., 2002) positive symptoms (Kaur et al., 2012a; Thonnessen et al., 2008), or hallucinations in particular (Fisher et al., 2008; Youn, Park, Kim, Kim, & Kwon, 2003). This type of variability may, in part, be due to small sample sizes, difficulty getting valid reports from patients during clinical interviews, and/or symptom attenuation following treatment with antipsychotic medication (Mathalon & Ford, 2012).

Inconsistency in the literature may point to the diversity of samples under study. Understanding the consequences of MMN reduction early in the illness will be facilitated by sorting patients according to their MMN amplitude and assessing known correlates of small MMN, such as functional impairment (Kawakubo et al., 2007; Light & Braff, 2005; Rasser et al., 2011), gray matter decline (Rasser et al., 2011; Yamasue et al., 2004), and increased symptom severity (Catts et al., 1995; Fisher et al., 2008; Javitt et al., 2000a;

Kasai et al., 2002; Youn et al., 2003). Further, detection of MMN deficits in subgroups of early illness schizophrenia patients may be improved by considering educational attainment, as less education has been associated with smaller MMN early in the illness (Umbricht et al., 2006). For these reasons, in addition to asking whether early illness patients experience deficits, clinically useful information might come from more investigation into *which* early illness patients experience deficits. Future research could investigate the manner in which different deviant types act as biomarkers for different functional and clinical deficits among recent onset patients. Moreover, longitudinal studies following patients from the prodromal period through more chronic phases of the illness could potentially clarify how deviant-specific MMN reductions evolve over the illness course.

Acknowledgements

References

Alho, K. (1995). Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear and Hearing, 16*, 38–51.

Atkinson, R. J., Michie, P. T., & Schall, U. (2012). Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. *Biological Psychiatry, 71*, 98–104.

Bodatsch, M., Ruhrmann, S., Wagner, M., Muller, R., Schultze-Lutter, F., Frommann, I., et al. (2011). Prediction of psychosis by mismatch negativity. *Biological Psychiatry, 69*, 959–966.

Brockhaus-Dumke, A., Tendolkar, I., Pukrop, R., Schultze-Lutter, F., Klosterkotter, J., & Ruhrmann, S. (2005). Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. *Schizophrenia Research, 73*, 297–310.

Catts, S. V., Shelley, A. M., Ward, P. B., Liebert, B., McConaghy, N., Andrews, S., et al. (1995). Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *The American Journal of Psychiatry, 152*, 213–219.

Crovitz, H. F., & Zener, K. (1962). A group-test for assessing hand- and eye-dominance. *American Journal of Psychotherapy, 75*, 271–276.

Csepe, V. (1995). On the origin and development of the mismatch negativity. *Ear and Hearing, 16*, 91–104.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*, 9–21.

Deouell, L. Y., Bentin, S., & Giard, M. H. (1998). Mismatch negativity in dichotic listening: Evidence for interhemispheric differences and multiple generators. *Psychophysiology, 35*, 355–365.

Devrim-Ucok, M., Keskin-Ergen, H. Y., & Ucok, A. (2008). Mismatch negativity at acute and post-acute phases of first-episode schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 258*, 179–185.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured clinical interview for DSM-IV axis I disorders (SCID), research version, patient edition with psychotic screen*. New York, NY: Biometrics Research, New York State Psychiatric Institute.

Fischer, C., Morlet, D., Bouchet, P., Luaute, J., Jourdan, C., & Salord, F. (1999). Mismatch negativity and late auditory evoked potentials in comatose patients. *Clinical Neurophysiology, 110*, 1601–1610 (Official journal of the International Federation of Clinical Neurophysiology).

Fisher, D. J., Labelle, A., & Knott, V. J. (2008). The right profile: Mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. *Clinical Neurophysiology, 119*, 909–921 (Official journal of the International Federation of Clinical Neurophysiology).

Fisher, D. J., Labelle, A., & Knott, V. J. (2012). Alterations of mismatch negativity (MMN) in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness. *Schizophrenia Research, 139*, 237–245.

Friedman, T., Sehatpour, P., Dias, E., Perrin, M., & Javitt, D. C. (2012). Differential relationships of mismatch negativity and visual p1 deficits to premorbid characteristics and functional outcome in schizophrenia. *Biological Psychiatry, 71*, 521–529.

Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences, 360*, 815–836.

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology, 120*, 453–463 (Official journal of the International Federation of Clinical Neurophysiology).

Giard, M. H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. *Psychophysiology, 27*, 627–640.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55*, 468–484.

Hermens, D. F., Ward, P. B., Hodge, M. A., Kaur, M., Naismith, S. L., & Hickie, I. B. (2010). Impaired MMN/P3a complex in first-episode psychosis: Cognitive and psychosocial associations. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 34*, 822–829.

Higuchi, Y., Sumiyoshi, T., Seo, T., Miyanishi, T., Kawasaki, Y., & Suzuki, M. (2013). Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state. *PLoS ONE, 8*, e54080.

Hollingshead, A. (1975). *Four-factor index of social status*. New Haven, CT: Yale University.

Jahshan, C., Cadenhead, K. S., Rissling, A. J., Kirihara, K., Braff, D. L., & Light, G. A. (2012). Automatic sensory information processing abnormalities across the illness course of schizophrenia. *Psychological Medicine, 42*, 85–97.

Javitt, D. C., Doneshka, P., Zylberman, I., Ritter, W., & Vaughan, H. G., Jr. (1993). Impairment of early cortical processing in schizophrenia: An event-related potential confirmation study. *Biological Psychiatry, 33*, 513–519.

Javitt, D. C., Grochowski, S., Shelley, A. M., & Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. *Electroencephalography and Clinical Neurophysiology, 108*, 143–153.

Javitt, D. C., Shelley, A., & Ritter, W. (2000). Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clinical Neurophysiology, 111*, 1733–1737 (Official journal of the International Federation of Clinical Neurophysiology).

Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: Defining the pattern. *Archives of General Psychiatry, 57*, 1131–1137.

Kasai, K., Nakagome, K., Itoh, K., Koshida, I., Hata, A., Iwanami, A., et al. (2002). Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: A high-resolution event-related potential study. *The American Journal of Psychiatry, 159*, 546–553.

Kaur, M., Battisti, R. A., Ward, P. B., Ahmed, A., Hickie, I. B., & Hermens, D. F. (2011). MMN/P3a deficits in first episode psychosis: Comparing schizophrenia-spectrum and affective-spectrum subgroups. *Schizophrenia Research, 130*, 203–209.

Kaur, M., Battisti, R. A., Lagopoulos, J., Ward, P. B., Hickie, I. B., & Hermens, D. F. (2012). Neurophysiological biomarkers support bipolar-spectrum disorders within psychosis cluster. *Journal of Psychiatry & Neuroscience: JPN, 37*, 313–321.

Kaur, M., Lagopoulos, J., Ward, P. B., Watson, T. L., Naismith, S. L., Hickie, I. B., & Hermens, D. F. (2012). Mismatch negativity/P3a complex in young people with psychiatric disorders: A cluster analysis. *PLoS ONE, 7*, e51871.

Kaur, M., Lagopoulos, J., Lee, R. S., Ward, P. B., Naismith, S. L., Hickie, I. B., et al. (2013). Longitudinal associations between mismatch negativity and disability in early schizophrenia- and affective-spectrum disorders. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 46*, 161–169.

Kawakubo, Y., Kamio, S., Nose, T., Iwanami, A., Nakagome, K., Fukuda, M., Kato, N., Rogers, M. A., & Kasai, K. (2007). Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. *Psychiatry Research, 152*, 261–265.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*, 261–276.

Kiang, M., Braff, D. L., Sprock, J., & Light, G. A. (2009). The relationship between preattentive sensory processing deficits and age in schizophrenia patients. *Clinical Neurophysiology, 120*, 1949–1957 (Official journal of the International Federation of Clinical Neurophysiology).

Kirino, E., & Inoue, R. (1999). The relationship of mismatch negativity to quantitative EEG and morphological findings in schizophrenia. *Journal of Psychiatric Research, 33*, 445–456.

Korostenskaja, M., Dapsys, K., Siurkute, A., Maciulis, V., Ruksenas, O., & Kahkonen, S. (2005). Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 29*, 543–548.

Leucht, S., Samara, M., Heres, S., Patel, M. X., Woods, S. W., & Davis, J. M. (2014). Dose equivalents for second-generation antipsychotics: The minimum effective dose method. *Schizophrenia Bulletin, 40*, 314–326.

Levanen, S., Hari, R., McEvoy, L., & Sams, M. (1993). Responses of the human auditory cortex to changes in one versus two stimulus features. *Experimental Brain Research, 97*, 177–183.

Light, G. A., & Braff, D. L. (2005). Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. *The American Journal of Psychiatry, 162*, 1741–1743.

Magno, E., Yeap, S., Thakore, J. H., Garavan, H., De Sanctis, P., & Foxe, J. J. (2008). Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. *Biological Psychiatry, 64*, 385–391.

Mathalon, D. H., & Ford, J. M. (2008). Divergent approaches converge on frontal lobe dysfunction in schizophrenia. *The American Journal of Psychiatry, 165*, 944–948.

Mathalon, D. H., & Ford, J. M. (2012). Neurobiology of schizophrenia: Search for the elusive correlation with symptoms. *Frontiers in Human Neuroscience, 6*, 136.

Michie, P. T., Budd, T. W., Todd, J., Rock, D., Wichmann, H., Box, J., et al. (2000). Duration and frequency mismatch negativity in schizophrenia. *Clinical Neurophysiology, 111*, 1054–1065 (Official journal of the International Federation of Clinical Neurophysiology).

Molholm, S., Martinez, A., Ritter, W., Javitt, D. C., & Foxe, J. J. (2005). The neural circuitry of pre-attentive auditory change-detection: An fMRI study of pitch and duration mismatch negativity generators. *Cerebral Cortex, 15*, 545–551.

Mondragon-Maya, A., Solis-Vivanco, R., Leon-Ortiz, P., Rodriguez-Agudelo, Y., Yanez-Tellez, G., Bernal-Hernandez, J., et al. (2013). Reduced P3a amplitudes in antipsychotic naive first-episode psychosis patients and individuals at clinical high-risk for psychosis. *Journal of Psychiatric Research, 47*, 755–761.

Murphy, J. R., Rawdon, C., Kelleher, I., Twomey, D., Markey, P. S., Cannon, M., et al. (2013). Reduced duration mismatch negativity in adolescents with psychotic symptoms: Further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis. *BMC Psychiatry, 13*, 45.

Naatanen, R. (2000). Mismatch negativity (MMN): Perspectives for application. *International Journal of Psychophysiology, 37*, 3–10 (Official journal of the International Organization of Psychophysiology).

Naatanen, R., & Alho, K. (1995). Generators of electrical and magnetic mismatch responses in humans. *Brain Topography, 7*, 315–320.

Naatanen, R., & Kahkonen, S. (2009). Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: A review. *The International Journal of Neuropsychopharmacology, 12*, 125–135.

Naatanen, R., Teder, W., Alho, K., & Lavikainen, J. (1992). Auditory attention and selective input modulation: A topographical ERP study. *NeuroReport, 3*, 493–496.

Naatanen, R., Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity (MMN): Towards the optimal paradigm. *Clinical Neurophysiology, 115*, 140–144 (Official journal of the International Federation of Clinical Neurophysiology).

Naatanen, R., Jacobsen, T., & Winkler, I. (2005). Memory-based or afferent processes in mismatch negativity (MMN): A review of the evidence. *Psychophysiology, 42*, 25–32.

Naatanen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clinical Neurophysiology, 118*, 2544–2590 (Official journal of the International Federation of Clinical Neurophysiology).

Nagai, T., Tada, M., Kirihara, K., Araki, T., Jinde, S., & Kasai, K. (2013). Mismatch negativity as a translatable brain marker toward early intervention for psychosis: A review. *Frontiers in Psychiatry, 4*, 115.

Nagai, T., Tada, M., Kirihara, K., Yahata, N., Hashimoto, R., Araki, T., et al. (2013). Auditory mismatch negativity and P3a in response to duration and frequency changes in the early stages of psychosis. *Schizophrenia Research, 150*, 547–554.

Nolan, H., Whelan, R., & Reilly, R. B. (2010). FASTER: Fully automated statistical thresholding for EEG artifact rejection. *Journal of Neuroscience Methods, 192*, 152–162.

Oades, R. D., Wild-Wall, N., Juran, S. A., Sachsse, J., Oknina, L. B., & Ropcke, B. (2006). Auditory change detection in schizophrenia: Sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. *BMC Psychiatry, 6*, 7.

Oknina, L. B., Wild-Wall, N., Oades, R. D., Juran, S. A., Ropcke, B., Pfueller, U., et al. (2005). Frontal and temporal sources of mismatch negativity in healthy controls, patients at onset of schizophrenia in adolescence and others at 15 years after onset. *Schizophrenia Research, 76*, 25–41.

Paavilainen, P., Alho, K., Reinikainen, K., Sams, M., & Naatanen, R. (1991). Right hemisphere dominance of different mismatch negativities. *Electroencephalography and Clinical Neurophysiology, 78*, 466–479.

Paavilainen, P., Simola, J., Jaramillo, M., Naatanen, R., & Winkler, I. (2001). Preattentive extraction of abstract feature conjunctions from auditory stimulation as reflected by the mismatch negativity (MMN). *Psychophysiology, 38*, 359–365.

Paavilainen, P., Valppu, S., & Naatanen, R. (2001). The additivity of the auditory feature analysis in the human brain as indexed by the mismatch negativity: 1 + 1 approximately 2 but 1 + 1 + 1 < 3. *Neuroscience Letters, 301*, 179–182.

Perez, V. B., Ford, J. M., Roach, B. J., Woods, S. W., McGlashan, T. H., Srihari, V. H., et al. (2012). Error monitoring dysfunction across the illness course of schizophrenia. *Journal of Abnormal Psychology, 121*, 372–387.

Perez, V. B., Woods, S. W., Roach, B. J., Ford, J. M., McGlashan, T. H., Srihari, V. H., et al. (2014). Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: Forecasting psychosis risk with mismatch negativity. *Biological Psychiatry, 75*, 459–469.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Jr., et al. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology, 37*, 127–152.

Rahne, T., von Specht, H., & Muhler, R. (2008). Sorted averaging—Application to auditory event-related responses. *Journal of Neuroscience Methods, 172*, 74–78.

Rasser, P. E., Schall, U., Todd, J., Michie, P. T., Ward, P. B., Johnston, P., et al. (2011). Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. *Schizophrenia Bulletin, 37*, 131–140.

Saarinen, J., Paavilainen, P., Schoger, E., Tervaniemi, M., & Naatanen, R. (1992). Representation of abstract attributes of auditory stimuli in the human brain. *NeuroReport, 3*, 1149–1151.

Salisbury, D. F., Shenton, M. E., Griggs, C. B., Bonner-Jackson, A., & McCarley, R. W. (2002). Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Archives of General Psychiatry, 59*, 686–694.

Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Archives of General Psychiatry, 64*, 521–529.

Schroger, E. (1995). Processing of auditory deviants with changes in one versus two stimulus dimensions. *Psychophysiology, 32*, 55–65.

Shaikh, M., Valmaggia, L., Broome, M. R., Dutt, A., Lappin, J., Day, F., et al. (2012). Reduced mismatch negativity predates the onset of psychosis. *Schizophrenia Research, 134*, 42–48.

Shelley, A. M., Ward, P. B., Catts, S. V., Michie, P. T., Andrews, S., & McConaghy, N. (1991). Mismatch negativity: An index of a preattentive processing deficit in schizophrenia. *Biological Psychiatry, 30*, 1059–1062.

Stephan, K. E., Baldeweg, T., & Friston, K. J. (2006). Synaptic plasticity and dysconnection in schizophrenia. *Biological Psychiatry, 59*, 929–939.

Stevens, J. C., & Hall, J. W. (1966). Brightness and loudness as functions of stimulus duration. *Perception & Psychophysics, 1*, 319–327.

Takegata, R., Paavilainen, P., Naatanen, R., & Winkler, I. (1999). Independent processing of changes in auditory single features and feature conjunctions in humans as indexed by the mismatch negativity. *Neuroscience Letters, 266*, 109–112.

Tervaniemi, M., Maury, S., & Naatanen, R. (1994). Neural representations of abstract stimulus features in the human brain as reflected by the mismatch negativity. *NeuroReport, 5*, 844–846.

Thonnessen, H., Zvyagintsev, M., Harke, K. C., Boers, F., Dammers, J., Norra, C., et al. (2008). Optimized mismatch negativity paradigm reflects deficits in schizophrenia patients. A combined EEG and MEG study. *Biological Psychology, 77*, 205–216.

Todd, J., Michie, P. T., Schall, U., Karayanidis, F., Yabe, H., & Naatanen, R. (2008). Deviant matters: Duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. *Biological Psychiatry, 63*, 58–64.

Todd, J., Michie, P. T., Schall, U., Ward, P. B., & Catts, S. V. (2012). Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction—Error generation, estimation or salience? *International Journal of Psychophysiology, 83*, 222–231 (Official journal of the International Organization of Psychophysiology).

Todd, J., Whitson, L., Smith, E., Michie, P. T., Schall, U., & Ward, P. B. (2014). What's intact and what's not within the mismatch negativity system in schizophrenia. *Psychophysiology, 51*, 337–347.

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia: A meta-analysis. *Schizophrenia Research, 76*, 1–23.

Umbricht, D. S., Bates, J. A., Lieberman, J. A., Kane, J. M., & Javitt, D. C. (2006). Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biological Psychiatry, 59*, 762–772.

Valkonen-Korhonen, M., Purhonen, M., Tarkka, I. M., Sipila, P., Partanen, J., Karhu, J., et al. (2003). Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Brain Research. Cognitive Brain Research, 17*, 747–758.

van Zuijen, T. L., Sussman, E., Winkler, I., Naatanen, R., & Tervaniemi, M. (2004). Grouping of sequential sounds—An event-related potential study comparing musicians and nonmusicians. *Journal of Cognitive Neuroscience, 16*, 331–338.

Wolff, C., & Schroger, E. (2001). Human pre-attentive auditory change-detection with single, double, and triple deviations as revealed by mismatch negativity additivity. *Neuroscience Letters, 311*, 37–40.

Yamasue, H., Yamada, H., Yumoto, M., Kamio, S., Kudo, N., Uetsuki, M., et al. (2004). Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia. *NeuroImage, 22*, 720–727.

Youn, T., Park, H. J., Kim, J. J., Kim, M. S., & Kwon, J. S. (2003). Altered hemispheric asymmetry and positive symptoms in schizophrenia: Equivalent current dipole of auditory mismatch negativity. *Schizophrenia Research, 59*, 253–260.