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Abnormal auditory pattern perception in schizophrenia

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ABSTRACT

Mismatch negativity (MMN) in response to deviation from physical sound parameters (e.g., pitch, duration) is reduced in individuals with long-term schizophrenia (Sz), suggesting deficits in deviance detection. However, MMN can appear at several time intervals as part of deviance detection. Understanding which part of the processing stream is abnormal in Sz is crucial for understanding MMN pathophysiology. We measured MMN to complex pattern deviants, which have been shown to produce multiple MMNs in healthy controls (HC). Both simple and complex MMNs were recorded from 27 Sz and 27 matched HC. For simple MMN, pitch- and duration-deviants were presented among frequent standard tones. For complex MMN, patterns of five single tones were repeatedly presented, with the occasional deviant group of tones containing an extra sixth tone. Sz showed smaller pitch MMN ($p = 0.009$, ~110 ms) and duration MMN ($p = 0.030$, ~170 ms) than healthy controls. For complex MMN, there were two deviance-related negativities. The first (~150 ms) was not significantly different between HC and SZ. The second was significantly reduced in Sz ($p = 0.011$, ~400 ms). The topography of the late complex MMN was consistent with generators in anterior temporal cortex. Worse late MMN in Sz was associated with increased emotional withdrawal, poor attention, lack of spontaneity/conversation, and increased preoccupation. Late MMN blunting in schizophrenia suggests a deficit in later stages of deviance processing. Correlations with negative symptoms measures are preliminary, but suggest that abnormal complex auditory perceptual processes may compound higher-order cognitive and social deficits in the disorder.

1. Introduction

Schizophrenia is associated with auditory abnormalities, including auditory verbal hallucinations and sensory perceptual deficits. Individuals with schizophrenia show reduced neural responses in auditory event-related potential (ERP) studies (Rosburg et al., 2008; Salisbury et al., 2009), suggesting abnormal cortical sensory-perceptual processing.

One such ERP component, mismatch negativity (MMN), is robustly reduced in long-term schizophrenia (for a review see Umbricht and Krljes, 2005). MMN appears in response to infrequent deviant stimuli, for example, rare 1.2 kHz tones played among 1 kHz standard tones. MMN amplitude correlates with the ability to match two tones after a short delay, and both MMN and tone matching thresholds are reduced in schizophrenia (Javitt et al., 2000). Therefore, reduction in MMN amplitude may indicate a deficit in detecting deviant stimuli in schizophrenia; however, the mechanisms behind MMN generation are debated.

MMN was originally proposed to reflect pre-attentive sensory-memory (Näätänen, 1990). More recently, MMN was re-conceptualized into a computational model of error-detection (Winkler, 2007; Winkler et al., 2009) where parts of auditory cortex form predictions about the auditory environment. Predictions feed-back to sensory areas and are compared to the incoming signal. MMN reflects prediction error, used to update the predictive model. The error-detection model of MMN therefore reflects communication between (at least) two separate cortical modules (sensory-memory related that may be dissociable from sensory responses, and cognitive). While MMN is typically reported to be around 150 ms after deviant-onset, several studies have reported multiple MMNs at later time intervals (~350 ms; Zachau et al., 2005; Korpilahti et al., 2001), indicating an auditory system hierarchy (Escera and Malmierca, 2014; Grimm and Escera, 2012).

One theory for MMN generation posits that MMN reflects release from stimulus-specific adaptation (SSA). According to this theory, MMN is essentially a large, delayed N1 response to a new deviant tone (May and Tiitinen, 2007, 2010). Single cell recordings have found SSA and MMN both increase in amplitude with decreased stimulus probability (Ulanovsky et al., 2003). However, SSA and N1 originate from temporal lobe (Javit et al., 1994; Hari et al., 1980), whereas MMN may originate from outside primary auditory cortex (Korzyukov et al., 1999; Rosburg et al., 2004). Enlarged N1 also does not explain how MMN has been reported outside of the N1 time window. Although

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SSA/N1 may contribute to simple MMN responses, and may contribute to the sensory-memory component of deviance detection, there is likely a second separate source, which may reflect a cognitive component.

Deviation from complex-patterns also evokes MMN. Measuring "complex" MMN responses may better elucidate deficits in the underlying mechanisms of deviance detection dysfunction in schizophrenia, by avoiding release from SSA, and isolating the cognitive component of deviance detection. Complex MMN has been reported in healthy populations. For example, deviant groups of five tones compared to standard groups of six produce complex MMN, suggesting that deviants from purely temporal patterns can evoke MMN, even when no stimulus is presented (Salisbury, 2012). MMN to deviant paired-tones also appeared at the expected 140 ms time window, but there was a second MMN reported at 350 ms (Zachau et al., 2005). MMN to language deviants also produced the expected MMN at 150 ms, but also a second MMN around 400 ms (Korpilahti et al., 2001), creating the possibility of an early (perhaps sensory-memory) MMN that is separate to a later (perhaps cognitive) MMN.

Little work has investigated complex MMN in schizophrenia. Alain et al. (1998) found no significant reduction in MMN (~150 ms) in schizophrenia to a complex pattern comprising two alternating tones, with the occasional repeated tone as a deviant. Rudolph et al. (2015) extended their previous findings by measuring MMN to a missing stimulus in schizophrenia, and found, compared to controls, significantly blunted MMN (~150 ms) in individuals who are in their early course psychosis. These results are inconclusive, highlighting the need for further exploration of complex MMN in schizophrenia.

We measured complex MMN to an extra sixth tone among groups of five tones. We predicted that the Gestalt principle of grouping by proximity would lead to a predictive coding model of five tones per group, and that a sixth tone would generate complex MMN due to violation of the abstract model. All tones were the same pitch and duration, hence ruling out any release from SSA. In fact, since the deviant was an extra repeated tone, adaptation demands that any evoked response should be smaller. We predicted that individuals with schizophrenia would show reduced complex MMN compared to controls, particularly in late MMN, indicating a deficit in the detection of deviation from a complex perceptual grouping rule.

2. Methods and materials

2.1. Participants

Twenty-seven participants with schizophrenia (Sz) were compared with 27 healthy control (HC) participants. Sz had at least 5 years length of illness or were hospitalized at least three times for psychosis. Twenty-two Sz had a diagnosis of schizophrenia (undifferentiated = 7; paranoid = 7; residual = 7; disorganized = 1), five had schizoaffective disorder (bipolar = 3; depressed = 2).

All subjects had normal hearing as assessed by audiometry, at least nine years of schooling, and an estimated IQ over 85. None of the participants had a history of concussion or TBI with sequelae, history of alcohol or drug addiction, or detox in the last five years, or neurological or psychiatric comorbidity. Groups were matched for age, gender, handedness, estimated premorbid IQ, and parental socioeconomic status (Table 1).

All participants provided informed consent after receiving a complete description of the study, and were paid for participation. Procedures were approved by the University of Pittsburgh IRB.

2.2. Diagnostic assessments

Diagnosis was based on the Structured Clinical Interview for DSM-IV (SCID-P). Symptoms were rated using the Positive and Negative Symptom Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS), and the brief UCSD Performance-based Skills Assessment (UPSA-B; for psychosocial functioning). All tests were conducted by an expert diagnostician. Sz were medicated, and moderately symptomatic.

2.3. Neuropsychological tests

All participants completed the MATRICS Cognitive Consensus Battery. Sz also completed the Brief Assessment of Cognition in Schizophrenia (BACS). In addition, all participants completed the Wechsler Abbreviated Scale of Intelligence (WASI), and the 4-factor Hollingshead Scale to measure socioeconomic status (SES) in the participant and in their parents. As expected, Sz had lower SES than HC, consistent with social and occupational impairment as a disease consequence.

2.4. Procedure

Stimuli were generated with Tone Generator (NCH Software), and presented in Presentation (Neurobehavioral Systems, Inc.). Binaural auditory stimuli were presented using Etymotic 3 A insert earphones, with loudness confirmed with a sound meter. Participants were instructed to concentrate on the silent movie and ignore the tones, which were played over earphones.

Table 1
Demographic and diagnostic information for the Sz and HC groups, with t/chi-square statistics and *p*-values for group comparisons. Medication is listed in Chlorpromazine (CPZ) equivalents.

	Sz		HC		Statistics
Age	36.00	(7.85)	32.44	(11.2)	$t(52) = 1.34, p = 0.185$
Gender	16 M/11 F		14 M/13 F		$x^2(3) = 0.03, p = 0.584$
% right handed	25 R/2 L		23 R/4 L		$x^2(3) = 0.59, p = 0.442$
SES	34.08	(13.96)	42.41	(11.1)	$t(52) = 2.66, p = 0.010$
Parental SES	37.69	(13.41)	42.30	(12.7)	$t(52) = 1.61, p = 0.113$
IQ	99.81	(18.78)	104.85	(8.3)	$t(52) = 1.28, p = 0.206$
MATRICS	50.96	(16.41)	57.19	(5.7)	$t(52) = 2.14, p = 0.037$
Medication (CLZ mg/day)	799.26	(648.53)			
Length of illness (days)	775.28	(439.96)			
PANSS total	63.00	(21.91)			
PANSS positive	16.15	(6.27)			
PANSS negative	17.54	(5.30)			
SAPS (global items)	3.59	(3.17)			
SAPS (symptom items)	8.81	(9.97)			
SANS (global items)	11.26	(3.34)			
SANS (symptom items)	33.93	(8.96)			
UPSA communication	78.70	(13.07)			
UPSA financial	85.61	(13.11)			

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