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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.

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,