Alterations of complex mismatch negativity (cMMN) elicited by a two-tone pattern paradigm in early-phase psychosis

Emma M.L. Ells, Erica D. Rudolph, Lauren Sculthorpe-Petley, Shelagh C. Abriel, Debra J. Campbell, Philip G. Tibbo, Derek J. Fisher

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ABSTRACT

The mismatch negativity (MMN) is a component of the event-related potential (ERP) elicited by a change in auditory stimulation (e.g., the occurrence of a deviant sound that violates the rules or regularities of the preceding stimulus sequence) regardless of whether one is attending to the change or not. As such, the MMN provides a useful index of pre-attentive cognition. While decreases in MMN amplitude are robustly observed in chronic schizophrenia, these deficits are less consistently present at the early phase of the illness. The current study utilizes a two-tone pattern paradigm that requires more complex computations than typical oddball stimulus presentations, which may be more appropriate for elucidating MMN deficits in an early phase psychosis (EP) sample. The stimuli were a standard sequence consisting of two alternating tones with different frequencies (e.g., ABABAB...), with MMN-eliciting pattern violations created by repetitions of either the A or the B tone. EEG recordings of 15 EP participants and 12 healthy controls (HCs) were collected. While no between-group differences were observed, MMN amplitudes in the EP group were correlated with positive and negative psychosis symptom scores. Follow-up analysis stratifying EP participants according to illness duration showed a reduced MMN amplitude in EP participants with a longer (2+ years) duration of illness, but not in EP participants who were within the first year of illness. These findings suggest a two-tone pattern paradigm may be useful in characterizing MMN-indexed cortical impairment later in the early phase of the illness, but not at first episode.

1. Introduction

1.1. Schizophrenia

Schizophrenia (SZ) is a uniquely devastating disease, typically emerging during young adulthood (Saha, Chant, Welham, & McGrath, 2005). Affecting about 1% of the population, SZ is characterized by alterations in cognition, affect, and behavior. As of yet, there is no cure for SZ and although recovery can occur in a small percentage of subjects, the majority of individuals will experience degrees of illness expression throughout their lifespan (Saha et al., 2005). Given the severity of the illness and the relative lack of understanding of the mechanisms that underlie it, there has been a significant research effort to elucidate the factors that contribute to SZ, as with more targeted treatment approaches better outcomes can result.

1.2. Mismatch negativity (MMN)

One area of developing research within SZ is the study of automatic, or pre-attentive, sensory perception. Difficulty organizing information early in the course of sensory processing may result in altered coordination of cortical activity and downstream deficits in cognitive function (Jahshan et al., 2012). One of the most efficient ways to probe basic automatic sensory functioning is with the electroencephalogram (EEG), a measure of neuroelectric brain activity that is typically measured non-invasively at the scalp, and EEG-derived event-related potential (ERP) components elicited in response to the presentation of discrete stimuli. One ERP component, the auditory mismatch negativity (MMN), is especially useful for measuring automatic sensory perception as it occurs very early in the sensory processing sequence, does not require any behavioural response, and can be elicited in the absence of attention to the stimuli (Naätänen, 2003). In its simplest form, the
MMN is thought to reflect preconscious detection of change in the auditory environment, and has been used as an index of central auditory function (Näätänen, Paavilainen, Rinne, & Alho, 2007). In order to detect this change, the auditory system must first form representations of the repetitive elements of auditory stimulation, against which incoming sounds are compared. Building on this conceptualization, updated models of the MMN posit it is elicited by any violation of an auditory regularity. Though typically elicited within an auditory oddball sequence, the MMN can be elicited by pattern paradigms wherein a commonly repeated pattern forms the auditory regularity (or ‘standard’) and any violation of (or deviation from) this pattern is recognized as a ‘mismatch’ in the predicted sequence, thereby eliciting an MMN.

1.3. Complex MMN

There has been some criticism that single-feature stimulus change paradigms such as the auditory oddball or the ‘optimal’ multi-feature paradigm (Näätänen, Pakarinen, Rinne, & Takegata, 2004), where the standard stimuli are physically identical and deviant stimuli contain a single changed feature, elicit both an MMN and an overlapping N100 enhancement (Jääskeläinen et al., 2004; Jacobsen & Schroger, 2001). As the deviant stimulus is presented much less often than the standard, the N100 elicited by deviant tones is much larger than the blunter refractory response that is evoked by standard tones, and the difference in their amplitudes is retained in the difference wave. While the MMN is almost certainly due to the detection of auditory irregularity rather than simply due to the firing of fresh afferents (Garrido, Kilner, Stephan, & Friston, 2009; Naatanen, Jacobsen, & Winkler, 2005), in such cases, the MMN and N100 can overlap and summate, and unravelling their relative contributions to the difference wave is often not possible without careful control procedures. In response to these concerns, there has been a movement to explore MMNs elicited by more complex stimulation parameters that avoid the sensory refractoriness problem that is inherent in the oddball paradigm.

One such paradigm is the two-tone pattern that has recently been explored by Sculthorpe and Campbell (2011); this paradigm has a standard sequence consisting of two alternating tones with different tonal frequencies (e.g. ABABAB…). MMN-eliciting pattern violations are then created by repetitions of either the A or the B tone (e.g. AABABAAB…). Since a deviant stimulus in this paradigm is physically identical to the standard stimulus that precedes it, the purported N100 elicited by the deviant stimuli is expected to be diminished (Sculthorpe & Campbell, 2011) while still producing a robust MMN (Sculthorpe, 2002; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006) and one reported increased MMN in UHR children (Bruggemann, Stockill, Lenroot, & Laurens, 2013). A recent meta-analysis reported no significant effect in MMNs elicited by frequency deviants, and a small-to-medium effect when duration deviants were used in first-episode psychosis (Haigh, Coffman, & Salisbury, 2017). Conversely, another meta-analyses reported first episode patients to exhibit a reduced MMN compared to healthy controls, but a significantly smaller effect size relative to those with chronic schizophrenia (Erickson, Ruffle, & Gold, 2016). It is of note that all of these previous studies have used traditional oddball paradigms. A paradigm requiring more complex computations may be more appropriate for consistently elucidating auditory change detection deficits early in the progression of the illness (Salisbury, 2012).

1.4. Mismatch negativity in Schizophrenia

Research into the MMN in SZ 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 (Coffman, Haigh, Murphy, & Salisbury, 2017; Javitt, Doneshka, Ritter, & Vaughan, 1993; Näätänen & Kahkonen, 2009; Umbricht et al., 2003), especially to duration deviants (Michie, 2001). There is an extensive literature suggesting that MMN deficits appear to be present at first episode (Hermens et al., 2010; Kaur et al., 2011; Oades et al., 2006; Solis-Vivanco et al., 2014) and may even predate psychosis in ultra-high risk (UHR) individuals (Atkinson, Michie, & Schall, 2012; Perez et al., 2014; Solis-Vivanco et al., 2014), with some groups reporting duration MMN deficits in UHRs being predictive of first episode psychosis within 2–5 years (Bodatsch et al., 2011; Higuchi et al., 2013; Shaikh et al., 2012; Shin et al., 2015). Despite the promise that the MMN offers as a diagnostic tool (Bodatsch, Brockhaus-Dumke, Kosterkotter, & Ruhrmann, 2015), these results are inconsistent. Brockhaus-Dumke et al. (2005) found that prodromal subjects showed a non-significant reduction of MMN amplitude which ranged in between healthy controls (HCs) and individuals with SZ, while other groups have reported a normal MMN at first break (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007; Salisbury, Polizzotto et al., 2017; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006) and one reported increased MMN in UHR children (Bruggemann, Stockill, Lenroot, & Laurens, 2013). A recent meta-analysis reported no significant effect in MMNs elicited by frequency deviants, and a small-to-medium effect when duration deviants were used in first-episode psychosis (Haigh, Coffman, & Salisbury, 2017). Conversely, another meta-analyses reported first episode patients to exhibit a reduced MMN compared to healthy controls, but a significantly smaller effect size relative to those with chronic schizophrenia (Erickson, Ruffle, & Gold, 2016). It is of note that all of these previous studies have used traditional oddball paradigms. A paradigm requiring more complex computations may be more appropriate for consistently elucidating auditory change detection deficits early in the progression of the illness (Salisbury, 2012).

1.5. Complex MMN in Schizophrenia

There is a small, but compelling, literature exploring cMMNs elicited by pattern paradigms in schizophrenia. One study used a complex pattern paradigm where a sequence of five identical tones formed the standard group, with the deviant being the inclusion of an additional (i.e. 6th) tone (Haigh, Coffman, Murphy, Butera, & Salisbury, 2016). Results showed two separate time windows; the first time window (~150 ms) produced similar MMN amplitudes for both SZ patients and controls, while the second time window (~400 ms) showed a significantly reduced negative deflection in SZ patients when compared to healthy controls. In contrast to the additional tone deviant, Salisbury and McCathern (2016) used a missing stimulus deviant, where a group of six identical tones acted as the standard group and deviant groups consisted of either a missing 4th or missing 6th tone. Results showed healthy control participants to have a small but robust cMMN to the missing stimuli, while this response was entirely absent in the SZ group. It is notable, however, that these studies report cMMN deficits in chronic SZ populations, which also exhibit robust deficits during simple stimulus-feature change paradigms.

The first study to use a pattern paradigm to elicit the cMMN in an early phase psychosis (EP) population was conducted by Rudolph et al. (2015). This study employed the same missing stimulus paradigm as described in Salisbury and McCathern (2016) and found cMMN amplitudes for the missing 4th stimulus to be significantly reduced in EP participants compared to healthy controls. Subsequently, Salisbury, McCathern et al. (2017) looked at patients within two months of first
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