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Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia

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ABSTRACT

Mismatch negativity (MMN) deficits in schizophrenia (SCZ) have been studied extensively since the early 1990s, with the vast majority of studies using simple auditory oddball task deviants that vary in a single acoustic dimension such as pitch or duration. There has been a growing interest in using more complex deviants that violate more abstract rules to probe higher order cognitive deficits. It is still unclear how sensory processing deficits compare to and contribute to higher order cognitive dysfunction, which can be investigated with later attention-dependent auditory event-related potential (ERP) components such as a subcomponent of P300, P3b. In this meta-analysis, we compared MMN deficits in SCZ using simple deviants to more complex deviants. We also pooled studies that measured MMN and P3b in the same study sample and examined the relationship between MMN and P3b deficits within study samples. Our analysis reveals that, to date, studies using simple deviants demonstrate larger deficits than those using complex deviants, with effect sizes in the range of moderate to large. The difference in effect sizes between deviant types was reduced significantly when accounting for magnitude of MMN measured in healthy controls. P3b deficits, while large, were only modestly greater than MMN deficits ($d = 0.21$). Taken together, our findings suggest that MMN to simple deviants may still be optimal as a biomarker for SCZ and that sensory processing dysfunction contributes significantly to MMN deficit and disease pathophysiology.

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1. Introduction

1.1. Mismatch negativity deficits in schizophrenia

Mismatch negativity (MMN), a component of the auditory event-related potential (ERP) is among the most widely studied biomarker of cognitive dysfunction in schizophrenia. It is typically elicited in response to an auditory oddball paradigm in which repeating standard stimuli are interrupted by infrequent deviants, which can range from simple deviants such as changes in pitch to violations of complex patterns or abstract rules (Näätänen et al., 2001). MMN is elicited even when the stimulus is not attended and when no behavioral response is required such as during sleep or coma (Kane et al., 1993; Sallinen et al., 1994), suggesting that it indexes a primarily pre-attentive stage of auditory information

processing. At the local circuit level, recent theories of MMN generation suggest critical involvement of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors, somatostatin interneurons, and theta-frequency generation mechanisms (Javitt et al., 2000a, 2000b; Javitt and Sweet, 2015; Lavoie et al., 2008; Michie et al., 2016; Umbricht et al., 2000).

Despite the well-replicated findings regarding MMN dysfunction in schizophrenia (Erickson et al., 2016; Umbricht and Krljes, 2005a), ideal approaches for eliciting MMN in clinical settings remain to be determined. In addition, relatively few studies have addressed the relationship between auditory sensory dysfunction and higher order cognitive impairment. Finally, while several studies have addressed potential contributions of neuroscientific constructs such as top-down vs. bottom-up processing to across-study heterogeneity of MMN findings, few have evaluated the potential contributions of technical issues such as absolute MMN amplitude or signal-to-noise. Here we use a meta-analytic approach to evaluate optimal utilization of MMN in the investigation of schizophrenia.

1.2. Deviant complexity

The earliest studies of MMN deficit in SCZ used simple deviants such as duration (Lembregts and Timsit-Berthier, 1993; Shelley et al., 1991)

Abbreviations: MMN, mismatch negativity; SCZ, schizophrenia; HC, healthy controls; ERP, evoked response potential or event-related potential; SOA, stimulus onset asynchrony.

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and pitch (Javitt et al., 1993). Since then, MMN deficits to both pitch and duration have been extensively replicated. For example, two meta-analyses have examined MMN deficits to simple deviants and found moderate to large effect sizes with duration deviants demonstrating the greatest deficit (Erickson et al., 2016; Umbricht and Krljes, 2005). Newer studies have also used more complex deviant types to assess MMN deficit in SCZ (Chen et al., 2016; Haigh et al., 2016; Hay et al., 2015; Kantrowitz et al., 2015; Rudolph et al., 2015; Salisbury and McCathern, 2016).

In both humans and animal models, neurophysiological evidence of deviance detection exists along much of the central auditory pathway, including brainstem structures such as inferior colliculus, medial geniculate nucleus, primary and secondary auditory cortex, and inferior frontal regions (Escera and Malmierca, 2014; Recasens et al., 2012). In general, responses to deviants in physical stimulus parameters are thought to activate deviant detectors at lower levels of the auditory system, while more complex MMN paradigms activate higher brain regions.

Prior meta-analyses in schizophrenia have focused primarily on MMN to simple physical deviants. However, several studies have now evaluated MMN from complex paradigms as well. Given an increased interest in studies using complex deviants, one goal of this meta-analysis is to evaluate the relative utility of simple vs. complex paradigms for evaluation of MMN dysfunction in SCZ.

1.3. Relationship between MMN and cognitive impairments in SCZ

A second set of unanswered questions concerns the relationship between MMN deficits and higher order cognitive impairments. Despite the simplicity of the MMN paradigm, effect sizes for MMN dysfunction are similar to those for impairments in overall cognitive function probed through standard neuropsychological measures (Schaefer et al., 2013) or with late ERP components such as P300 that require both attention and cognitive control (Linden, 2005; Perlman et al., 2015; Polich, 2007). A subcomponent of P300, P3b, is elicited when subjects are asked to respond to rare deviants in the auditory oddball paradigm and is also impaired in SCZ (Jeon and Polich, 2003; Leitman et al., 2010; Perlman et al., 2015). Pre-attentive deviance detection is a processing step required for subsequent planned responses to attended deviants (Novak et al., 1992). Therefore, deficits in MMN may limit the ability to generate a normal P3b response (Javitt et al., 1995).

In some studies, MMN and P3b have been measured in the same subjects and this within-subject design promises to reveal the relationship between the two measures and their relative deficits. For example, Leitman et al. (2010) used structural equation modeling and a combination of traditional and adaptive threshold paradigms to quantify the contribution of MMN to P3b. MMN deficits to pitch deviants accounted for about 50% of the deficit in P3b. We performed an additional meta-analysis specific to studies that obtained both MMN and P3b in parallel to evaluate the relative magnitude of deficit and the relationship between the two measures.

1.4. The influence of signal-to-noise

MMN paradigms have yet to be standardized across research sites studying SCZ. Even in HC, there can be considerable variability in MMN amplitude and signal-to-noise based on differences in data collection (recording equipment, environment, auditory stimulus paradigm) and data analysis methods (electrode referencing, peak detection routine). Some of the variation between studies in MMN deficit is likely due to these differences in signal-to-noise detection of the MMN component in HC. We hypothesize that techniques and paradigms that generate more robust MMN in HC are more likely to detect deficits in SCZ. Conversely, any loss of MMN signal could result in reduced group differences. Therefore, we also examined the relationship between MMN amplitude in HC and MMN deficit in SCZ across all studies and conditions.

To date, approaches to eliciting MMN in SCZ have varied substantially across research groups. An overall goal of this meta-analysis is to facilitate increased convergence and standardization toward optimal paradigms in SCZ.

2. Materials and methods

2.1. Literature search

We searched PubMed and a recent meta-analysis on mismatch negativity in schizophrenia (Erickson et al., 2016). In addition, one study under submission for this issue was also included (Perrin et al., 2017). Studies were only included if they were peer-reviewed original articles with data not previously reported elsewhere, if they included both a healthy control group and a patient group (>75% schizophrenia spectrum disorders group), and if mismatch negativity during a passive auditory oddball task was quantified using EEG in both groups and reported as mean \pm SD/SE (or attainable visually from published figures) or groups were compared pairwise using *t*-test/ANOVA (*t*-stat, *F*-stat, Cohen's *d*, or *p*-value). Twin studies were excluded with the exception of a separate search for studies measuring both MMN and P3b in HC and SCZ. Studies were also excluded if reporting of methodology was inadequate (e.g. electrode site or latency window not reported) or if there was significant evidence that data quality was poor. Only one study was excluded for both incomplete reporting of methodology and poor data quality (Li et al., 2013).

Literature search was performed in multiple steps. First, all studies included in Erickson et al. (2016) were reviewed. We included all articles from that meta-analysis except those that did not examine a schizophrenia spectrum disorder group, as that was beyond the scope of this study (e.g. studies that only examined bipolar disorder, relatives of schizophrenia patients, or clinical high risk group). We also excluded studies in which MMN was measured under an active paradigm in which the subject attended to or responded to the deviants used to calculate the MMN waveform.

With respect to psychotic disorders, we were more inclusive than the Erickson et al. (2016) meta-analysis, allowing for inclusion of schizoaffective disorder or studies in which a patient group consisted of >75% of patients in a schizophrenia spectrum disorder category (brief psychotic disorder, schizophreniform disorder, delusional disorder, schizoaffective disorder, schizophrenia, or first episode psychosis later confirmed to be schizophrenia spectrum). Given this inclusivity, we also reviewed all studies excluded by Erickson et al. (2016) for reason of "unclear diagnostic group" and included those that met our diagnostic criteria.

In some cases, MMN means and SDs were obtainable from visual measurement of published bar graphs/scatter plots that showed means and variance information. Therefore, we also reviewed studies excluded for "insufficient data" and included those in which MMN mean and SD was ascertainable. In one case of "insufficient data" we were able to contact the study author who provided data tables for inclusion into our meta-analysis (Laton et al., 2014).

Next, we performed our own PubMed keyword search limited to 2015 and later to include more recent studies, as some of these were studies that would not have been captured by Erickson et al. (2016). We used a Boolean logic combination of the following keyword terms: ["schizophrenia" OR "schizoaffective" OR "psychosis"] AND ["mismatch negativity" OR "MMN" OR "N2a"]. This yielded 73 hits of which 61 were excluded, leaving 12 studies included from 2015 to present, including Perrin et al. (2017).

We were also interested in including studies examining more complex deviant types beyond simple duration, pitch, and intensity deviants. Therefore, we performed a PubMed keyword search of all years up to the present (January 2017) that focused on complex deviants using the following terms: ["schizophrenia" OR "schizoaffective" OR "psychosis"] AND ["mismatch negativity" OR "MMN" OR "N2a"] AND

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