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Meta-analysis and systematic review of the literature characterizing auditory mismatch negativity in individuals with autism

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ABSTRACT

A number of past studies have used mismatch negativity (MMN) to identify auditory processing deficits in individuals with autism spectrum disorder (ASD). Our meta-analysis compared MMN responses for individuals with ASD and typically developing controls (TD). We analyzed 67 experiments across 22 publications that employed passive, auditory-based MMN paradigms with ASD and TD participants. Most studies lacked design characteristics that would lead to an accurate description of the MMN. Variability between experiments measuring MMN amplitude was smaller when limited to studies that counterbalanced stimuli. Reduced MMN amplitude was found among young children with ASD compared to controls and in experiments that used non-speech sounds. Still, few studies included adolescents or those with below-average verbal IQ. Most studies suffered from small sample sizes, and aggregating these data did not reveal significant group differences. This analysis points to a need for research focused specifically on understudied ASD samples using carefully designed MMN experiments. Study of individual differences in MMN may provide further insights into distinct subgroups within the heterogeneous ASD population.

1. Introduction

Autism Spectrum Disorder (ASD) is characterized by impairments in social communication and interaction as well as by the presence of repetitive and restricted behaviors or interests, including atypical responses to sensory stimuli like sounds (American Psychiatric Association, 2013). Language impairments, while not core symptoms in ASD, often co-occur (Tager-Flusberg et al., 2005). Atypical responses to auditory stimuli and difficulty in learning spoken language are linked to disruptions of auditory filtering, acoustic feature discrimination, sound source identification, and auditory working memory (Anderson & Kraus, 2010; Foss-Feig et al., 2012; Näätänen et al., 2012; O'Connor, 2012). Given that these processes are vital components of auditory processing, several researchers have hypothesized that in ASD, there is a common disruption in neural networks that govern basic auditory processing (Bomba and Pang, 2004; Marco et al., 2011). To pinpoint the underlying bases of atypical auditory processing in brain-based disorders, researchers often turn to measures like electroencephalography (EEG) and magnetoencephalography (MEG). These neuroelectric imaging approaches have the temporal resolution necessary to track neural activity associated with specific auditory events, thereby providing a window into auditory processing not afforded by other non-invasive neural measures[1]. Here, a meta-analysis was undertaken to determine the extent to which neural response that reflect acoustic feature discrimination and auditory working memory in early auditory processing differs in ASD relative to typical development (TD).

We focused on one common approach that can capture such features of early auditory processing: the mismatch negativity (MMN) paradigm (Näätänen et al., 2012; Näätänen et al., 2007). The MMN measures an individual's ability to detect changes in auditory patterns by presenting a regularly occurring, "standard" pattern that is interrupted at random with rare, "deviant" stimuli (Näätänen et al., 1978). Deviant stimuli usually differ perceptually from standards on a single acoustic feature, such as intensity, pitch, or phoneme. Typically, the unexpected, rare sounds elicit neural responses not present when that same sound is expected. The size of those neural responses indexes the degree to which a listener has built up a memory trace of an ongoing auditory pattern and detected a deviation from that trace (Näätänen et al.,

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[1] For reviews of prior research utilizing neural measures to investigate atypical auditory processing in brain-based disorders like ASD, Specific Language Impairment, Dyslexia, Learning impairment, Schizophrenia, Attention-Deficit/Hyperactivity Disorder, Bipolar Disorder, and Aphasia, see: Aaltonen et al. (1993); Barry et al. (2003); Bishop (2007); Chitty et al. (2013); Erickson et al. (2015); Kraus et al. (1996); Kujala et al. (2013); Näätänen and Kähkönen (2009); O'Connor (2012); Umbricht and Krljesb (2005).

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2007). It has been argued that this neural response is driven by NMDA receptor activity in the bilateral auditory and frontal cortices (Näätänen et al., 2012). MMN components can be well detected on the scalp's frontal-central midline using EEG and can be quantified as a negative component that occurs 100 to 250 ms following a deviant stimulus onset (Haesen et al., 2011). In source space, the mismatch field arises from frontal and supratemporal generators during a similar time window (Giard et al., 1990; Novak et al., 1990).

The MMN component itself is calculated from the difference between the response evoked by the same event when it is a standard and when it is a deviant. By directly comparing responses to identical stimuli when they are expected versus when they are deviants, the MMN in a baseline-corrected measure, revealing neural activity driven by hearing an unexpected event. Response latency of the MMN is determined based on the timing of the negative peak in the difference waveform. Response amplitude can be computed by taking the average response in a window centered on this negative peak. However, the analysis window used to determine MMN amplitude and latency varies across studies (e.g., it can be based on each individual subject's waveform, based on the average waveform of each subject group, or based on the average from all participants). Both MMN amplitude and latency metrics signify rapid discrimination that is driven by both bottom-up automatic and top-down attentive processes at early stages of cortical processing (Näätänen et al., 2012; Roberts et al., 2011).

The MMN response can be elicited both during active tasks, where the subject makes an overt response upon detecting the deviant stimulus, and in settings when the subject listens passively, with no overt response required. As such, the MMN is one of the few established neural measures of auditory processing that does not require a high degree of instruction, overt attention, or active participation from the research participant (Bishop, 2007; Näätänen et al., 2012). This makes the MMN attractive to researchers studying individuals with ASD, whose verbal and cognitive abilities range across a wide spectrum; for paradigms measured in an active setting that require subjects to follow instructions, pay attention to stimuli, or perform a behavioral task, variations in subjects' abilities undoubtedly affect the measured response. To make meaningful cross-group comparisons from experiments that include subjects with and without verbal and cognitive deficits, it is important to use a paradigm for which performance is not significantly influenced by attention or other higher-level cognitive processes.

Many passive MMN experiments have been conducted on the ASD population, but there is no consensus across studies as to whether or not people with ASD exhibit a different MMN response to auditory deviants. Some publications have reported heightened and/or earlier MMN responses to acoustic deviants in ASD, suggesting greater auditory sensitivity to changes in acoustic stimuli (Gomot et al., 2011; Lepistö et al., 2007). Other publications have reported suppressed and/or delayed MMN responses to acoustic deviants in ASD, indicating a weaker sensitivity (Andersson et al., 2013; Yu et al., 2015). Still others have reported mixed results, such that some deviant stimuli elicit group differences while others do not (Lepistö et al., 2005; Lepistö et al., 2008). While several past reviews have described these conflicting findings (Foss-Feig et al., 2012; Haesen et al., 2011; Kujala et al., 2013; Mcfadden and Rojas, 2013; Näätänen and Kujala, 2011; O'Connor, 2012; Orekhova and Stroganova, 2014), none have critically evaluated which factors may account for similarities and discrepancies across studies.

This lack of consensus prompted us to conduct a meta-analysis exploring whether there are methodological or stimulus differences that explain apparent inconsistencies across studies. We compared MMN response amplitude and MMN response latency between individuals with ASD and age-matched TD controls. We compiled the results from all experiments that met our inclusion criteria into a comprehensive statistical framework, treating each experiment or statistic as a single data point in our analysis. Given the complexities of collecting EEG and MEG data from individuals with ASD, sample sizes in individual studies tended to be fairly small and lacked strong power on their own. Our meta-analysis synthesized results across studies, thereby increasing the statistical power when testing for group differences.

We began by analyzing all published experiments that measured group differences between ASD and TD participants using either MMN amplitude or latency in a passive, auditory-based MMN paradigm. We then narrowed our analysis to include only those experiments that controlled for general variation in event-related potential or event-related field (ERP/ERF) responses to different stimulus tokens. Specifically, we only included studies in which the MMN was calculated by comparing responses to identical stimuli presented in two different contexts – one in which they were unexpected deviants and the other in which they were expected standards. Without counterbalancing stimuli in this way, any difference in signal morphology between the response to deviants and standards might be due to differences in the unrelated neural responses to the specific stimuli presented, such as a loud sound producing a larger ERP/ERF than a soft sound (Duncan et al., 2009; Kujala, 2007). We followed up with analyses examining how stimulus characteristics (speech versus nonspeech sounds) impacted group-difference effect size and whether participant characteristics (age and verbal reasoning) influenced the findings.

2. Methods

2.1. Literature search and screening criteria

Our meta-analysis and systematic review followed PRISMA guidelines (Moher et al., 2009). We began with a comprehensive literature search to identify publications reporting experiments that measured auditory MMN components in individuals with ASD, using the key terms "MMN," "MMF", "mismatch negativity," "mismatch field," "oddball," "autism," and "ASD" on PubMed, ScienceDirect, and Google Scholar. We used the following inclusion criteria:

(1) The publication had to include an experiment that used a paradigm in which standard stimuli were more prevalent than the interspersed deviant(s).
(2) The publication had to include an experiment that collected data with EEG or MEG.
(3) The publication had to include a passive listening experiment; specifically, participants must have received no instructions to listen and must not have been required to provide a behavioral response (such as a hand raise or lever press) to detected deviant stimuli. This requirement reduces any influence of top-down modulation of neural responses, allowing for a fair comparison of neural responses from TD listeners and the more heterogeneous ASD sample, which included listeners with cognitive deficits.

2.2. Inclusion criteria for meta-analysis

Following our initial screening of publications, we established additional criteria for the inclusion of publications in our meta-analysis (Fig. 1). The publication had to include an experiment that reported means, variation of the mean (i.e., standard error or standard deviation of the mean), and sample sizes of either MMN amplitude or latency for both an ASD and a TD comparison group. These descriptive statistics were necessary to calculate effect sizes for the meta-analysis. If any of this information was missing from the publication, we contacted authors of studies published between 2011–2017[2] and invited them to provide us with that information. Experimental statistics that compared participants with ASD to participants with other neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder, receptive developmental language disorder, tuberous sclerosis, dyslexia) were not

[2] Individual correspondence with authors was needed in two instances to receive unpublished, additional information.