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A Meta-Analysis of Mismatch Negativity in Schizophrenia: From Clinical Risk to Disease Specificity and Progression

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ABSTRACT

BACKGROUND: The observation that mismatch negativity (MMN) is consistently impaired in schizophrenia has generated considerable interest in the use of this biomarker as an index of disease risk and progression. Despite such enthusiasm, a number of issues remain unresolved regarding the nature of MMN impairment. The present study expands upon an earlier meta-analysis of MMN impairment in schizophrenia by examining impairment across a range of clinical presentations, as well as across experimental parameters.

METHODS: One hundred one samples of schizophrenia patients were included in the present study, including first-episode (n = 13), chronic (n = 13), and mixed-stage (n = 75) samples. Additionally, MMN was examined in three related conditions: bipolar disorder (n = 9), unaffected first-degree relatives (n = 8), and clinical high risk (n = 16).

RESULTS: We found that MMN impairment 1) likely reflects a vulnerability to disease progression in clinical high-risk populations rather than a genetic risk for the condition; 2) is largely unrelated to duration of illness after the first few years of illness, indicating that impairment is not progressive throughout the life span; 3) is present in bipolar disorder, albeit to a lesser degree than in schizophrenia; and 4) is not modulated by experimental parameters such as magnitude of change between standard and deviant tones or frequency of deviant tones but may be modulated by attentional demands.

CONCLUSIONS: Such findings lay the foundation for a better understanding of the nature of MMN impairment in schizophrenia, as well as its potential as a clinically useful biomarker.

Keywords: Bipolar disorder, High risk, Meta-analysis, Mismatch negativity, Prodromal, Schizophrenia

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The mismatch negativity (MMN) is an event-related potential that has garnered attention in recent years for its promise as a biomarker for schizophrenia. The MMN is an electrophysiological response that is elicited when a sequence of identical auditory stimuli is infrequently interrupted by a stimulus that deviates from the standard stimulus along one or more dimensions, such as pitch, duration, or intensity. This event-related potential therefore appears to represent the automatic change detection process that occurs when an acoustic event violates expectations maintained by the active auditory trace [for a review, see (1)]. People with schizophrenia exhibit robust and reliable deficits in MMN production (2), a finding that motivates interest in this phenomenon as a putative index of structural impairment in the frontal and temporal cortices (3–5), as a target to validate the clinical and biological relevance of pharmacologic compounds (6), and, more recently, as a predictor for conversion to psychosis among high-risk individuals (7,8).

Given such enthusiasm for this index, recently hailed as a breakthrough biomarker for understanding and treating psychosis (9), a next logical step is to use a meta-analytic approach to evaluate what is known about MMN impairment in schizophrenia and provide clarity on issues that have yet to be resolved. One such unresolved issue relates to the progressive nature of MMN impairment. It has been suggested that MMN impairment worsens over the course of the illness (10,11), an observation that is modestly supported by a trend-level association between MMN impairment and illness duration in an earlier meta-analysis (12). Such findings are consistent with reports of elevated rates of gray matter loss in schizophrenia (13). However, one large study that explicitly tested this hypothesis found that although the MMN tends to decrease in amplitude with age for both groups, the magnitude of group difference was not substantially larger for those individuals at later stages of the illness (14) [see also (15)]. It is therefore unclear whether MMN impairment reflects a stable feature of the illness or if it follows a progressive course.

A second issue concerns the degree to which MMN impairment is associated with illness state and/or genetic predisposition for developing schizophrenia. Recently, there has been considerable enthusiasm for the use of MMN to predict conversion to psychosis among at-risk individuals. However, it is not yet known whether MMN impairment is associated with the emergence of symptoms specifically or

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reflective of genetic risk for developing the disorder. To date, the literature indicates that MMN impairment is greater among high-risk samples that later convert to schizophrenia (8,16,17) but has also been observed among unaffected first-degree relatives (REL) of schizophrenia patients (18). Therefore, it is not yet clear whether MMN impairment represents an index of an emerging illness or is better conceptualized as an endophenotype marker of genetic vulnerability.

A related issue concerns the specificity of MMN impairment to schizophrenia, as compared with bipolar disorder (BP). To date, the literature is mixed regarding support for MMN impairment in bipolar disorder [for a review, see (19)]. However, there is increasing evidence that bipolar patients share many of the cognitive deficits found in schizophrenia patients (20), as well as substantial symptom overlap among bipolar patients with psychotic features. Therefore, it is of interest to know whether MMN impairment is diagnosis-specific or if it is better conceptualized within the Research Domain Criteria framework as an impairment that is shared across psychotic disorders.

Finally, disagreement remains regarding the role of impaired auditory discrimination on MMN decrements in schizophrenia. For instance, one study reported that group differences in MMN amplitude were minimized when tone pairs were matched to individuals' auditory discrimination thresholds, a phenomenon that may be accounted for by floor effects in MMN amplitude as the standard-deviant difference becomes smaller (21). However, it has also been demonstrated that the most robust between-group differences emerge when the change in stimulus characteristics between standard and deviant stimuli is large, rather than small (22). If impaired auditory discrimination meaningfully impacts the magnitude of the mismatch response in schizophrenia patients, the effect sizes of MMN impairment ought to be largest when the difference between standard and deviant stimuli is the most difficult to detect [see (23,24)]. However, the observation that this is not the case suggests that early sensory processing deficits may not be a primary constraint on MMN amplitude in schizophrenia.

The purpose of the present study was to expand upon a previous meta-analysis (12) by exploring the pattern of MMN impairment across multiple levels of risk for psychosis, as well as across the course of the illness. Furthermore, we aimed to better understand the nature of impoverished MMN production among schizophrenia patients by identifying experimental parameters that impact effect size estimates, such as deviant tone properties and attentional demands. Though some of these questions were explored by Umbricht and Krljes (12), this early meta-analysis was conducted using 36 schizophrenia patient samples that were available at the time. Here, we add 65 samples of schizophrenia patients, as well as 33 samples with related conditions including BP (n = 9 samples), clinical high risk (CHR) (n = 16 samples), and REL (n = 8 samples). The schizophrenia patient groups included first-episode schizophrenia or first-episode psychosis (SZ-F) (n = 13 samples), chronic schizophrenia patients (SZ-C) (n = 13 samples), and a broader category of patients that were not separated into illness stage by the experimenters (SZ-All) (n = 75 samples). Patient samples were assigned to first-episode and chronic groups only if they were identified as such by the authors of the original study. The present study is the first to directly compare MMN integrity across these different groups and therefore allows for 1) a comparison of MMN impairment across the spectrum of risk and disease progression, and 2) more power to detect relationships between effect size and experimental parameters.

METHODS AND MATERIALS

Literature Search and Study Selection

A literature search was conducted using Web of Science (Thompson Reuters Corporation, New York, New York) and PubMed (National Center for Biotechnology Information, National Institutes of Health, Bethesda, Maryland) (years 1987 to 2014) using combinations of the keywords schizophrenia, schizoaffective, psychosis, prodromal, bipolar disorder, mismatch negativity, and MMN. Furthermore, we examined reference lists from those studies for additional articles not identified in the original search. Only peer-reviewed manuscripts were considered. This initial search strategy identified 216 articles. The following criteria were then used to identify studies for inclusion in the meta-analysis: 1) the MMN amplitude must be reported as a difference wave (deviant minus standard event-related potential); 2) group differences in MMN amplitude must be reported either in terms of mean and standard deviation or as a t test or F test; 3) the study should include at least one psychiatrically healthy control group and one comparison group of schizophrenia or bipolar patients that have been diagnosed according to contemporary diagnostic standards (e.g., DSM-III or later, ICD-9 or later) or of individuals who have been identified as high risk for psychosis, prodromal, or first-degree relatives of schizophrenia patients; 4) for consistency, only electroencephalogram (not magnetoencephalogram) studies of MMN were included in the present analysis; and 5) only studies that presented original data (i.e., no reanalysis of previously published data) were included. Following the initial search, we discovered a small number of studies that examined MMN amplitudes among twin pairs. Given that these samples were likely characterized by dependencies that are not characteristic of the other included studies, the four twin studies were excluded.

Using these criteria, 104 unique articles were selected for inclusion in the meta-analysis (see Supplemental Table S1 for a list of studies and sample characteristics). Several of these studies included multiple patient comparison groups, yielding a total of 134 comparison samples that consisted of 13 SZ-F, 13 SZ-C, 75 SZ-All, 16 CHR, 9 BP, and 8 REL samples. For studies in which drug effects were evaluated or for which test-retest data were available, only the placebo/baseline condition was included in the present meta-analysis. In a small number of studies, the deviant types were very unusual and therefore were not included in the present analysis—for example, Todd *et al.* (25) used intensity-matched duration deviants as one of the experimental conditions. Given the unusual nature of these matched deviant stimuli, only the standard paradigm stimuli from these studies [see also (21)] were included. One hundred twelve of the 216 identified studies were rejected from the present analysis (Supplemental Table S2).