Research Paper

No association between symptom severity and MMN impairment in schizophrenia: A meta-analytic approach

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ABSTRACT

The mismatch negativity (MMN) is an event-related potential that is consistently attenuated in people with schizophrenia. Within the predictive coding model of psychosis, MMN impairment is thought to reflect the same prediction failures that are also thought to underlie the development and crystallization of delusions and hallucinations. However, the true relationship between symptom severity and MMN impairment across studies has not yet been established. The present meta-analysis used meta-regressions to examine the relationship between MMN impairment (quantified as Hedges' g) and PANSS positive and negative symptom totals across 62 and 68 samples, respectively. Furthermore, we examined the relationship between MMN impairment and group differences in educational achievement ($n = 47$ samples), cognitive ability ($n = 36$ samples), and age ($n = 86$ samples). Overall, we found no significant associations between MMN impairment and symptom severity (p's > 0.50); however, we did observe a trend-level association between MMN impairment and lower education ($p = 0.07$) and a significant association with older age ($p < 0.01$) in the schizophrenia patient group. Taken together, these results challenge a simple predictive coding model of psychosis, and suggest that MMN impairment may be more closely associated with premorbid functioning than with the expression of psychotic symptoms.

1. Introduction

Although hallucinations and delusions represent core features of schizophrenia, a viable explanatory model that accounts for these symptoms has not been forthcoming. Recently, there has been considerable interest in the *predictive coding* (PC) framework to conceptualize the emergence and maintenance of positive symptoms (Fletcher and Frith, 2009; Adams et al., 2013). PC posits that one's beliefs about the world (*posterior beliefs*) result from an integration of *prior beliefs* with incoming sensory information. A mismatch between what is expected (priors) and what is perceived generates a *prediction error* (PE) which then updates beliefs about future events. In the healthy brain, PEs serve to orient attention to events not accounted for by prior beliefs and motivate an update of those beliefs. In the context of psychotic symptoms, PC failures have been used to explain the formation and crystallization of delusions (Adams et al., 2013), as well as hallucinations (Horga et al., 2014). For example, inappropriate PE

signaling coincident with common events may imbue those events with added salience, spurring delusion formation (Kapur, 2002; Heinz, 2002; Corlett et al., 2007).

Despite the promising conceptual link between the PC framework and phenomenology, evidence supporting an association between experimentally-elicited PEs and symptom severity has not been consistently observed. For instance, there is considerable disagreement regarding the relationship between positive symptoms and mismatch negativity (MMN), an electrophysiological index of auditory processing that is commonly described as a prototypical PC phenomenon (e.g. Wacongne et al., 2012) and is robustly impaired in schizophrenia (Erickson et al., 2015). The MMN is an event-related potential elicited when a sequence of regular auditory stimulation is infrequently interrupted by a tone that deviates from the standard stimulus along one or more dimensions (e.g., pitch or duration). Within the context of the PC framework, the MMN can be conceptualized as a PE that is generated when the prior belief—expectation of a standard stimulus—is

violated by the presentation of a deviant tone. MMN production also appears to rely on the same biological processes that are thought to be involved in prediction formation and PE signaling. Glutamate disruption via administration of NMDA antagonists such as ketamine attenuates the MMN in humans (e.g. Umbricht et al., 2000; see also Rosburg and Kreitschmann-Andermahr, 2016 for a meta-analysis) and animals (Tikhonravov et al., 2008). PC theory posits that prior expectations are signaled top-down most commonly via NMDA receptors and PEs most commonly via AMPA receptors. The MMN may therefore be an important biomarker that links neurochemical disruption in schizophrenia with a cognitive model that accounts for the development of psychosis.

One proposed mechanism by which this relationship emerges is through weak development of priors following NMDA disruption. Insufficient priors may yield abnormally weak PEs that manifest as MMN impairment, as well as aberrant belief formation and sensory experiences. Accordingly, reports have emerged suggesting that MMN amplitude is indeed associated with hallucinations (Fisher et al., 2011), and positive symptoms in general (Kärgel et al., 2014; Fisher et al., 2014). However, a number of other reports failed to find a strong relationship (e.g. Baldeweg et al., 2002; Devrim-Üçok et al., 2008; Jahshan et al., 2012; Kim et al., 2014; Perez et al., 2014; Salisbury et al., 2002), including one study with over 800 participants in which the correlation between positive symptoms and MMN amplitude was only 0.08 (Light et al., 2015). Similarly, it has been reported that MMN amplitude is associated with negative symptom severity (Catts et al., 1995), although this observation has also been challenged by a number of failures to replicate these findings (e.g. Baldeweg and Hirsch, 2015; Devrim-Üçok et al., 2008; Dulude et al., 2010; Grzella et al., 2001; Horton et al., 2011; Perez et al., 2014). As a result, the relationship between MMN impairment and symptom severity is not well-understood.

In the present analysis we evaluate the PC theory of psychosis by taking a meta-analytic approach to measure the relationship between MMN and symptom severity. We would interpret a significant association between MMN effect size and symptom severity as strong support for the PC model of psychosis. In the event that MMN impairment is not associated with psychosis, a secondary aim of this work was to identify sample characteristics that *are* consistently associated with reduced MMN in schizophrenia. For instance, it has been suggested that MMN impairment may be more strongly associated with low premorbid IQ than with the emergence of psychosis (Salisbury et al., 2017). This suggestion is consistent with other reports of significant associations between cognitive ability and MMN amplitude (Hermens et al., 2010; Higuchi et al., 2013); however, the results from this literature are mixed, and a meta-analytic approach is necessary to determine the robustness of this association across studies.

We examined the relationship between MMN impairment and positive and negative symptoms across 68 studies, as well as the relationship between MMN impairment and educational achievement and cognitive ability across 47 and 36 samples, respectively. We found that MMN impairment was not significantly associated with either positive or negative symptoms, but did appear to be meaningfully associated with lower educational achievement and older age in the patient group compared to healthy participants. Finally, we discuss this pattern of results and its implications for how best to consider the MMN within the PC framework.

2. Methods

2.1. Literature search and study selection

The present meta-analysis is an extension of a recent meta-analysis examining MMN effect sizes by group, illness duration, and stimulus type (Erickson et al., 2015). As such, the search parameters were identical for the present study, inclusive of all peer-reviewed research

published through December 31, 2016. Briefly, the literature search was conducted through Web of Science (Thompson Reuters Corporation, New York, New York) and PubMed (National Center for Biotechnology Information, National Institutes of Health, Bethesda, Maryland) using the following search terms: schizophrenia, schizoaffective, psychosis, prodromal, bipolar disorder, mismatch negativity, and MMN (years 1987 to 2016). Although prodromal and bipolar samples were investigated in the previous study, they were not included in the present meta-analysis. Only peer-reviewed manuscripts written in English were considered. This initial search strategy identified 237 articles.

The following inclusion/exclusion criteria were then applied: (1) the MMN amplitude must be reported as a difference wave (deviant-minus-standard); (2) group differences in MMN must be reported either in terms of mean and standard deviation, *t*-test, *F*-test, effect size, or as a precise *p*-value; (3) the study must include at least one psychiatrically healthy control group and one comparison group of participants who have been diagnosed with a schizophrenia-spectrum disorder according to contemporary diagnostic standard (e.g., DSM-III or later, ICD-9 or later); (4) for consistency, only electroencephalogram (not magnetoencephalogram) studies of MMN were included in the present analysis; (5) only studies that presented original data were included; (6) only studies that reported symptom severity as a total or summary score from the PANSS or SAPS/SANS were included; and (7) only studies that reported educational achievement (in years) and/or cognitive test performance by group were included. Cognitive assessment tools such as the National Adult Reading Test (Nelson and Willison, 1991), subtests from the Wechsler Adult Intelligence Scale (Wechsler, 1997), and subtests from the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) were among the most commonly used assessments.

Finally, there were no additional inclusion/exclusion criteria for the healthy comparison sample, with the exception that they must not have a diagnosis of schizophrenia or bipolar disorder. A list of inclusion/exclusion criteria used by individual studies can be found in Supplementary Table 1.

Using these criteria, 84 unique articles were included in the meta-analysis (Supplementary Table 2). These 84 articles included 90 samples of patients with a schizophrenia-spectrum disorder, 16 of which were first episode (SZ-F), and 9 of which were chronic samples (SZ-C). The remaining samples were comprised of patients with mixed illness duration (SZ-All). Ten of the 90 samples (4 SZ-F; 6 SZ-All) included patients with other psychotic disorders, such as Psychosis NOS and Delusional disorder (see Supplementary Table 3 for a list of diagnoses). 153 articles were rejected from the meta-analysis (see Supplementary Table 4 for the list of studies and reasons for exclusion).

2.2. Effect size and meta-regression calculations

All effect size and meta-regression calculations were conducted using Comprehensive Meta-Analysis Software (Biostat, Inc., Englewood, New Jersey). Hedges' g (Hedges and Olkin, 1985) was used to estimate

Table 1
Demographic, clinical, and cognitive variables.

	Healthy controls	SZ-All	SZ-F	SZ-C
Total N	3526	3485	419	214
Age	32.07 (7.25)	35.14 (7.31)	23.40 (3.42)	34.88 (6.32)
Percent male	57.87% (15.54%)	68.46% (16.57%)	62.07% (16.03%)	75.96% (15.32%)
Education	14.56 (1.39)	12.63 (0.82)	11.11 (3.87)	12.72 (1.20)
Cognition (z-score)	–	− 0.89 (0.55)	− 1.55 (1.98)	− 1.42 (2.28)
PANSS positive	–	16.23 (3.22)	20.59 (2.70)	17.19 (1.15)
PANSS negative	–	18.61 (3.88)	22.12 (3.57)	18.79 (3.61)
Hedges' g	–	0.94	0.41	0.82

effect size, which is calculated as $(M_1 − M_2)/(SD_{pooled})$. For all included studies, Hedges' g was estimated on the basis of (1) group means and standard deviations; (2) *t*-tests or *F*-tests of the group effect; (3) *p*-value and sample size, or (4) Cohen's *d* and sample size. Many studies examined MMN amplitude across multiple deviant types, probabilities, and magnitudes; the effects of these stimulus parameters were explored in previous work (Erickson et al., 2015). For the present analysis, only the group effect across all levels of deviant type, magnitude, and probability was examined.

To examine the relationship between effect size and symptom severity, positive and negative symptom severity scores were regressed on Hedges' g in two separate meta-regressions. Symptom severity was quantified using PANSS positive and negative symptom subscales for majority of samples ($n = 42$). The SAPS and SANS was used for 20 and 26 samples, respectively; for these studies, PANSS positive and negative symptom equivalent scores were calculated using the following equations (developed by van Erp et al., 2014):

$$PANSS\ Positive = 11.1886 + (0.2587 * SAPS\ Total\ score)$$

$$PANSS\ Positive = 9.3264 + (1.1072 * SAPS\ Summary\ score)$$

$$PANSS\ Negative = 7.1196 + (0.3362 * SANS\ Total\ score)$$

$$PANSS\ Negative = 6.7515 + (1.0287 * SANS\ Summary\ score)$$

To examine the impact of cognitive ability on MMN effect size, two meta-regressions were conducted in which (1) difference in education (in years) was regressed on Hedges' g, and (2) the standardized difference in mean cognitive performance was regressed on Hedges' g. Given the variety of cognitive tests employed by different research groups, we were unable to estimate ability for individual cognitive domains; rather, a coarse index of cognition was calculated by averaging the patients' z-transformed cognitive performance across all neuropsychological tests in a given study. Given that most neuropsychological measures are substantially intercorrelated, we expect that this coarse metric provides an approximate measure of general cognitive ability. Information about educational achievement was available for 47 samples, and cognitive performance was reported for 36 samples. Of the 36 samples in which cognitive performance was measured, 13 completed a battery of neuropsychological assessments that assessed at least three cognitive domains. An additional, separate meta-regression was conducted on this subset of samples with a more thorough neuropsychological evaluation to further explore the relationship between cognitive impairment and MMN attenuation.

3. Results

3.1. Sample characteristics and effect size by group

The combined demographic, cognitive, and clinical information from all included studies is presented in Table 1. The average age for healthy, SZ-All, and SZ-C groups was 32 to 35 years, whereas the average age for SZ-F participants was 23 years. A larger percentage of participants was male in the psychosis groups (62%–76%) compared to the healthy control group (58%). On average, healthy control participants had two more years of education (14.56 years) compared to the psychosis groups (11.11–12.72 years). SZ-F participants exhibited more severe symptoms, as well as significantly reduced MMN impairment compared to the SZ-C and SZ-All groups, consistent with our previous report (p's < 0.05) (Erickson et al., 2015).

3.2. Symptom and cognitive variables and MMN impairment

Of the 90 samples included in the meta-analysis, 62 included a PANSS positive or SAPS score, and 68 included a PANSS negative or SANS score. The results of the meta-regressions between positive and negative symptom severity with MMN effect size are depicted in Fig. 1a
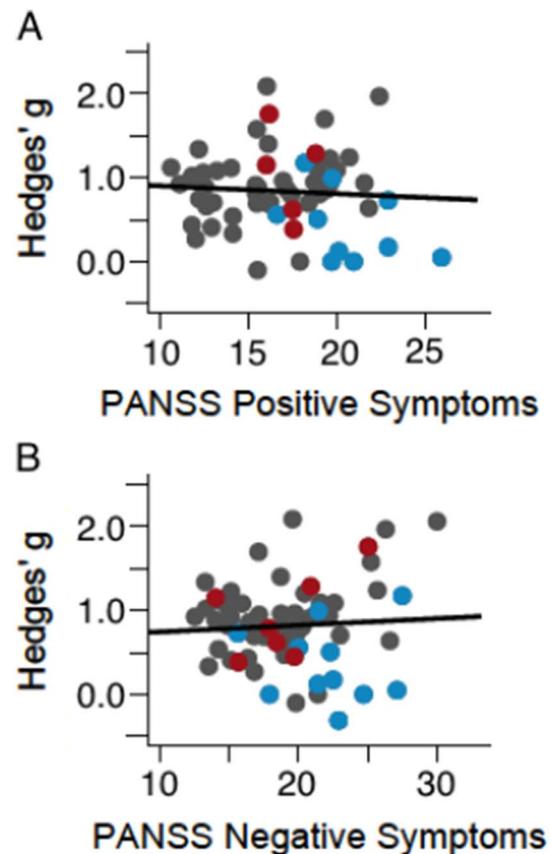

Fig. 1. Regression of positive symptoms on Hedges' g (A) and regression of negative symptoms on Hedges' g (B). Gray = SZ-All; Red = SZ-C; Blue = SZ-F. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and b, respectively. There was no significant association between symptom severity and MMN effect size for positive symptoms ($B = −0.01$, $p = 0.51$) or negative symptoms ($B = 0.01$, $p = 0.55$).

By contrast, there was a trend-level association between difference in education and MMN effect size ($B = 0.11$, $p = 0.07$; Fig. 2a). That is, the larger the difference in educational achievement, the larger the difference in MMN. Given that educational achievement is typically moderately correlated with cognitive ability, we would expect to see similar effects on measures of cognitive performance (36 samples). However, the relationship between cognition and effect size was not significant ($B = −0.01$, $p = 0.86$; Fig. 2b). Similar observations were made using the subset of 13 samples that received a more thorough cognitive assessment ($B = −0.25$, $p = 0.61$). Given the suggestive findings on educational achievement and the widely varying quality of cognitive assessment data across studies, we urge caution in accepting this null result. Additional large sample studies with adequate cognitive testing are needed to support more definitive conclusions.

Finally, because healthy control participants were three years younger than patient samples, on average, we conducted a final meta-regression examining the relationship between age disparity and MMN impairment (86 samples). Difference in age was significantly associated with MMN effect size ($B = −0.04$, $p < 0.01$; Fig. 3), with larger effect sizes associated with older patient samples compared to controls.

4. Discussion

The primary findings of the present study call into question the simple model of PC disruption that posits a direct relationship between MMN attenuation and the severity of psychosis. We found no significant
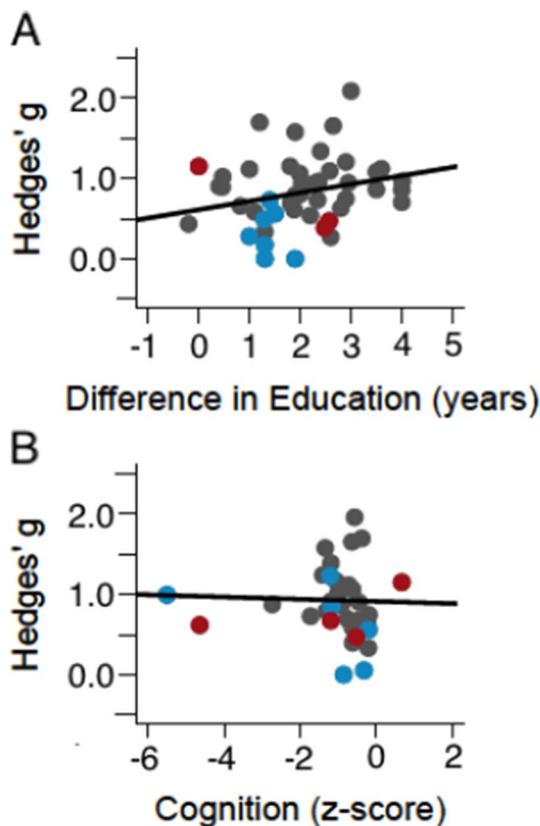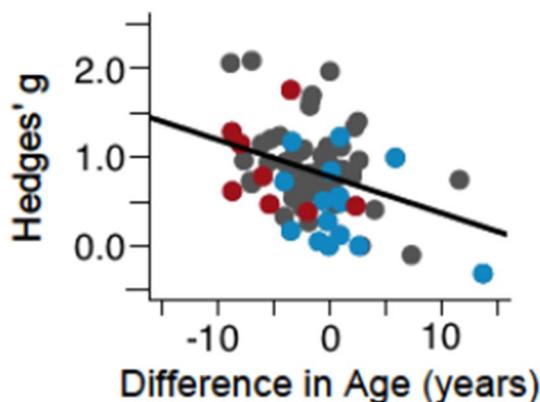
call for a deeper appreciation for the role of hierarchical representations and, taken in the context of other data, it appears that symptoms may be associated with higher levels of the hierarchy and more complex inferences than those engaged by the MMN.

Funding sources

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scog.2017.05.002.

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