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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.

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 (Lembreghts 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., 2018). 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 ± 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. (2018).

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

["complex" OR "abstract" OR "pattern" OR "missing"]. We also included any studies from Erickson et al. (2016) that included complex deviants as well as Perrin et al. (2018). This resulted in 24 studies included in the analysis of complex deviants.

Lastly, we wanted to examine the within-study relationship between MMN and P3b. Therefore, we performed a separate search of all years up to the present for studies that measured both ERPs in HC and SCZ. Our search consisted of the following combination of terms: ["schizophrenia" OR "schizoaffective" OR "psychosis"] AND ["mismatch negativity" OR "MMN" OR "N2a"] AND ["P300*" OR "P3" OR "P3a" OR "P3b"]. Only studies that measured P3b under an active auditory oddball paradigm where the deviant was a target stimulus requiring a response were included. Studies were only included if they measured both P3b and MMN in the same subject groups. Out of 100 studies found, 87 were excluded leading to 17 included.

Overall, a total of 117 studies were included. The number of population samples used in each analysis is reported in Section 3 (Results).

2.2. Data encoding

We encoded a number of variables of interest. First, we were interested in the effect size of MMN deficits in SCZ. Therefore, where available, we used the mean and SD of MMN for HC and SCZ (in μV). Preference was given to MMN measured in frontal and midline sites (electrode Fz) which for some studies included the mean of frontal or midline electrode chains but in some cases included the mean of all electrodes or the global field potential (GFP). Preference was also given to MMN measured in the difference waveform (deviant minus standard stimulus ERP) but in rare cases, studies only reported MMN from the deviant waveform. In some cases, the mean and SD was not available for each group but outcomes of a statistical analysis comparing HC vs. SCZ was reported (such as *t*-test or ANOVA). In such cases, we encoded in order of preference the F-stat, t-stat, Cohen's d, or *p*-value which in combination with the sample sizes could be used to derive the effect size and its confidence intervals (see Section 2.3). Some studies measured MMN using different deviant types, different analyses conditions, or in multiple patient groups. These were all entered separately to keep track of different patient samples and conditions. For a sub-group of studies that also measured P3b, a similar methodology was used to encode P3b results but preference was given to parietal and midline electrode sites and to analyses using the target waveform (in rare cases, only the difference waveform P3b was reported).

Mean age, percent male, and deviant type were all recorded for each sample. For deviant type, we encoded whether the deviant was a simple pitch, duration, or intensity deviant. There was significant variation in whether duration deviant tones were longer or shorter than the standard tones. Therefore, we also encoded duration deviant polarity (i.e. longer/shorter). We also encoded whether a deviant was a more complex sensory deviant such as a simple double, SOA, intra- or inter-tone gap, white noise, omission/missing, location, frequency glide/modulation, or non-vocal prosody deviant. In addition to complex sensory deviants, some deviants were more abstract, naturalistic, or involved changes in stimulation pattern. These were encoded separately as complex abstract/pattern deviants and included pattern (extra tone in a tone train or ascending vs descending frequency tone pairs), novel environmental sounds, or language deviants (vowel sounds).

2.3. Statistical analysis

Effect size was calculated by deviant type for simple deviants (pitch, duration, intensity). If MMN was measured under multiple deviance levels and probabilities for a given study and deviant type, preference was given to the condition with a deviance level and deviance probability closest to 10%. For each comparison of HC and SCZ, effect size was calculated by the difference between the means divided by the pooled standard deviation. The overall effect size was calculated using a meta-analysis fixed effects model (Berkey et al., 1995; Hedges and Olkin, 1985; Raudenbush, 2009; van Houwelingen et al., 2002), which provides an estimate of the overall effect size pooled across studies by properly averaging and weighting the uncertainty of effect sizes estimated from each individual study. For duration deviants, we calculated the overall effect size in longer and shorter deviants separately; in cases where both were measured for a given study, both were included in the calculation.

In addition to simple deviants, we computed overall effect size for complex sensory and complex abstract/pattern deviants separately. In some studies, the same sample was subjected to multiple complex deviants. Since we were interested in determining whether complex deviants could outperform simple deviants in detecting deficits in SCZ, we selected the specific deviant type and condition that maximized effect size. Because the complex deviant parameter space is larger and more multi-dimensional, this ensured that only complex deviants which optimized deficit detection were included. Some studies included both simple and complex deviants. To better account for across study variability, we performed an additional analysis of effect size measured using only studies in which both simple and complex deviants were used. For each study, the simple and complex deviant that maximized effect size was included only. This was done separately for studies that included complex sensory and complex abstract/pattern deviants. There were nine studies available for the complex sensory and five for the complex abstract/pattern analysis. The overall effect size was calculated for the simple deviant and corresponding complex deviant condition using the meta-analysis fixed effects model.

To examine the relationship between deficits in MMN and P3b in SCZ, we only included studies in which both were measured in the same study sample. Individual study effect size for P3b was calculated in the same way as for MMN, using the difference between the means divided by the pooled standard deviation. Only studies using simple deviants were included for this comparison. Overall effect size was calculated for MMN and P3b separately as well as an effect size comparing P3b deficits vs MMN deficits using the meta-analysis fixed effects model. A weighted linear regression with study sizes as weights was performed between P3b deficits and MMN deficits to obtain their correlation.

Finally, we examined the relationship between magnitude of MMN in HC and the deficit in MMN found in SCZ. For each study sample and condition comparing MMN in HC and SCZ, we calculated a normalized mean of MMN in HC (mean MMN divided by standard deviation) and the individual study effect size of MMN between SCZ and HC as the standardized mean difference between groups (mean difference divided by pooled standard deviation). This was possible when mean and SD were reported for the MMN of HC or the effect size could be derived from the reported *t*-statistic or F-statistic. Samples and conditions missing the needed HC data were not included. There were 202 data points included out of the 241 sample/condition combinations available. In addition, we ran both an unweighted analysis of variance (ANOVA) and analysis of covariance (ANCOVA) to test whether MMN amplitude in HC accounted for the difference in effect sizes between deviant types. We limited each sample to one deviant probability and level (closest to 10%) to better compare deviant categories. Deviant category was used as a factor and the normalized mean for MMN in HC was used as a covariate for the ANCOVA. We calculated the unadjusted and adjusted effect sizes for each deviant type. A similar but separate ANOVA/ANCOVA pair was run on duration deviant data points with one factor (longer/shorter duration deviant). In a separate analysis, we grouped simple deviants (pitch, duration, intensity) and complex deviants (abstract/pattern and complex sensory) together and performed a univariate ANOVA comparing simple versus complex. This was repeated after adjusting for MMN in HC (ANCOVA).

Meta-analyses were performed using R package "metafor" (Viechtbauer, 2010). All tests were two-sided at a significance level of 0.05. SPSS version 23 (IBM) was used to run ANOVA and ANCOVA tests. All other analyses were performed in R version 3.3.2.

3. Results

3.1. MMN deficits to simple deviants

The overall effect size of MMN to simple physical deviants (pitch, duration, and intensity) in SCZ vs HC was measured. The deficit to each deviant was analyzed separately (Fig. 1). There were 64, 88, and 8 samples included for pitch, duration, and intensity deviants, respectively (see Supplemental Table 1 for list of all studies included in this meta-analysis). Results are consistent with previous reports with all simple deviants demonstrating deficits in SCZ with moderate to large effect sizes. Also consistent with previous reports (Erickson et al., 2016; Umbricht and Krljes, 2005), duration deviants showed the largest effect size. The effect size to duration deviants was 24% larger than for pitch deviants.

Duration deviants can be presented as longer or shorter than standard stimuli. We examined whether the polarity of the duration deviance influenced effect size. As shown in Fig. 1, long duration deviants demonstrated a 26% larger effects size than shorter duration deviants. This result should be interpreted with caution, however, since the level of deviance may also influence the effect size. Long duration deviants differed from standards more than short duration deviants in both absolute duration and percent change (short duration: -43.9 ± 8.25 ms, $-60.7 \pm 13.3\%$; long duration: 69.0 ± 38.3 ms, $113 \pm 28.7\%$; $p = 0.0025$ for absolute duration, $p = 0.001$ for % change).

3.2. MMN deficits to complex deviants

Some studies have used more complex deviant types to elicit MMN. We divided these into two main categories. "Complex sensory" included paradigms in which deviants 1) varied in multiple sensory dimensions simultaneously, 2) depended on binaural vs. monaural processing or 3) utilized complex sounds. "Complex abstract/pattern" included paradigms in which simple physical features did not differentiate standards from deviants. Instead, for these paradigms deviance used to elicit MMN consisted of violations in patterns of stimulation, variation in abstract features or rules, or representation of changes in more naturalistic features (see Section 2.2).

Deficits in MMN to complex deviants likely rely more heavily on higher tier regions of the auditory stream, including secondary auditory regions and frontal cortex. In contrast, MMN deficits to deviation in sensory features likely rely on auditory cortical or even subcortical deviance detection. We measured the overall effect size of schizophrenia to complex sensory and complex pattern/abstract deviants (Figs. 2, 3). For population samples that were tested under multiple complex deviants, the deviant that maximized effect size was chosen. For both complex sensory and complex abstract/pattern deviants, effect sizes were moderate and comparable to those elicited by simple deviants. No evidence of preferential utility of these paradigms was detected.

To better account for across-study variability, we also calculated MMN effect size to simple and complex deviants using only studies that included both types of deviants. Only the simple and complex deviant conditions that maximized effect size were included to draw a fair comparison. For complex sensory deviants, there were nine studies available that also used simple deviants. The maximal overall effect size was 0.78 (95% CI 0.59–0.97) for simple deviants versus 0.46 (95% CI 0.27–0.64). There were only five studies that included both complex abstract and simple deviants. For those studies, the maximal overall effect size was 0.66 (95% CI 0.36–0.96) for simple deviants and 0.75 (95% CI 0.45–1.05). Therefore, although less studies were available, the within-study analysis was consistent with the broader analysis in showing no evidence of preferential utility of complex paradigms. More studies that include both simple and complex deviants are needed to confirm these findings in a larger sample.

3.3. P3b versus MMN deficits

We compared deficits in MMN to those of P3b in SCZ. We have previously suggested that a substantial component of deficits in higher order processing in SCZ, as reflected in P3b, may be attributable to sensory-level dysfunction (Leitman et al., 2010). Studies in which both were measured in the same population samples were included. The difference in effect size between P3b and MMN was calculated in each sample as well as the overall difference for all included 17 samples.

Only studies using simple deviants were included. In this sub-sample of studies, the overall effect size for MMN was 0.65 (95% CI: 0.53–0.78) and for P3b was 0.87 (0.74–1.00). As expected, the relative deficit in P3b was larger than that in MMN (Fig. 4). However, also consistent with prior expectation, the difference in effect size, 0.2 ± 0.16, is in the range of "small" as opposed to the deficit in MMN itself, which is in the range of moderate to large, demonstrating that sensory function and higher order processing deficits are similarly impaired in schizophrenia.

We also examined the degree to which P3b amplitude depended on prior MMN generation across studies (Fig. 5). As expected, there was a significant correlation between deficits in the two neurophysiological measures after adjusting for age and gender reflected by a correlation coefficient of 0.43 ($p = 0.04$). Thus, across studies MMN deficits accounted for 18.7% of the variance in P3b deficits. In general, MMN amplitude has shown correlation with some subsequent potentials such as the N2, but findings regarding MMN vs. P3 amplitude have been

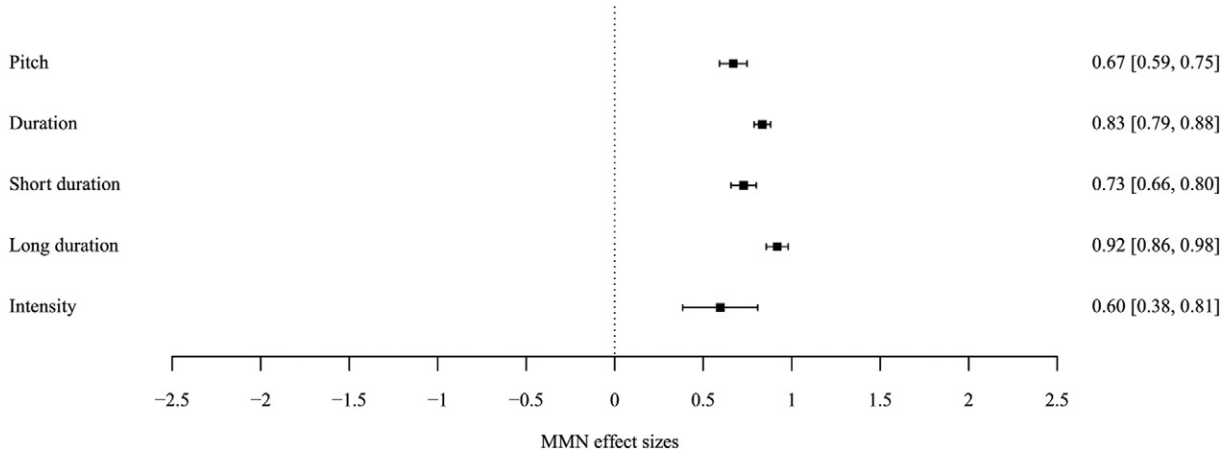

Fig. 1. MMN deficits in SCZ by deviant category. The overall pooled effect size calculated using a fixed effects model is shown with 95% confidence intervals (horizontal error bars) for each simple deviant category. Exact values are reported on the right column including confidence intervals in brackets. Longer and shorter duration deviants were also analyzed separately. Positive values indicate lower MMN magnitudes in SCZ.

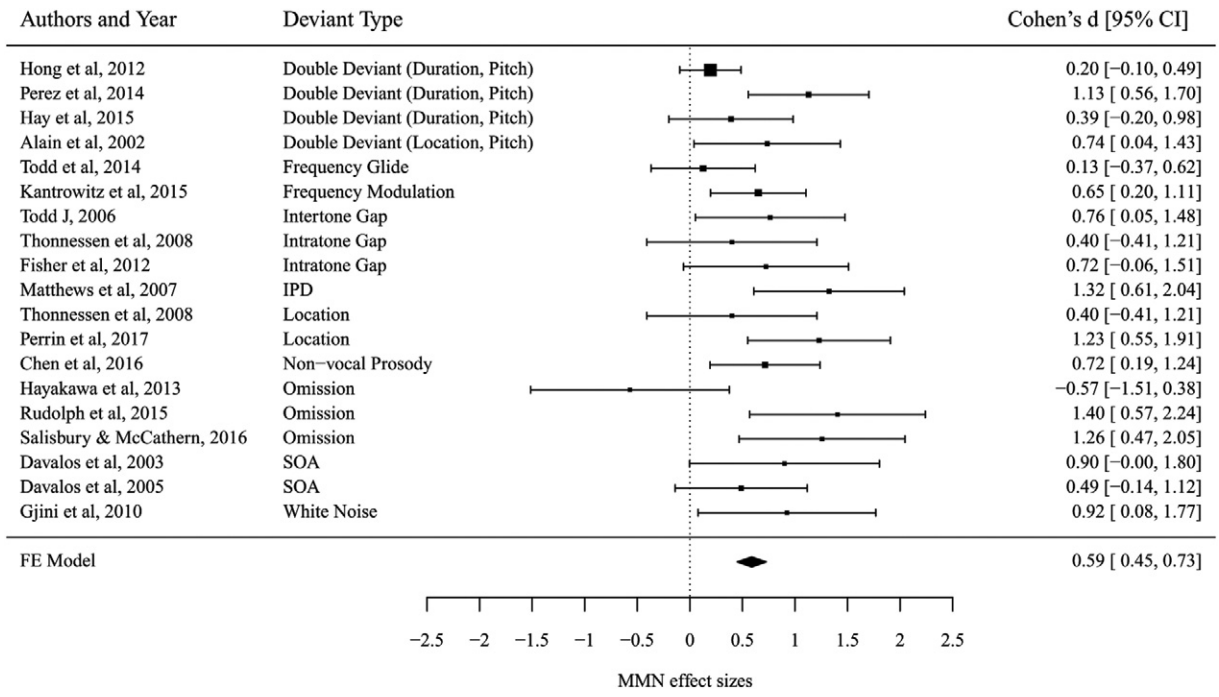

Fig. 2. MMN deficits in SCZ using complex sensory deviants. Effect sizes for individual HC vs SCZ study samples are shown for studies using complex sensory deviants (as defined in Section 2.2) with 95% confidence intervals plotted as horizontal error bars. The pooled effect size using a fixed effects model is shown at the bottom including its 95% confidence interval. Positive values indicate lower MMN magnitudes in SCZ.

variable (e.g. Leitman et al., 2010; Umbricht et al., 2006). The present study confirms a significant association between MMN and P3 based upon cross-study correlation.

3.4. MMN deficits in SCZ vs. MMN signal-to-noise

As detailed above, MMN can be measured in different patient populations, under different stimulation conditions (e.g. deviant types), and with different ERP analysis methods. Although differences in effect size across paradigms is typically interpreted relative to neuroscientific constructs, purely technical aspects such as magnitude and signal-to-noise of the MMN measure within the HC population may also contribute to differences in effect size of the observed deficit. It is axiomatic that to observe a deficit of MMN in SCZ, there must be a measurable level of MMN in HC. A larger MMN in HC leaves more room to detect a deficit in clinical groups. Therefore, we examined the relationship between MMN deficit (effect size in MMN in HC vs SCZ) and the normalized amplitude of MMN in HC (Fig. 6A).

MMN measurements from all studies under all conditions were included (223 data points). As predicted, larger normalized MMN amplitude in HC predicted more deficit in SCZ. This suggests that detecting deficits in SCZ using MMN is optimized by selecting conditions under

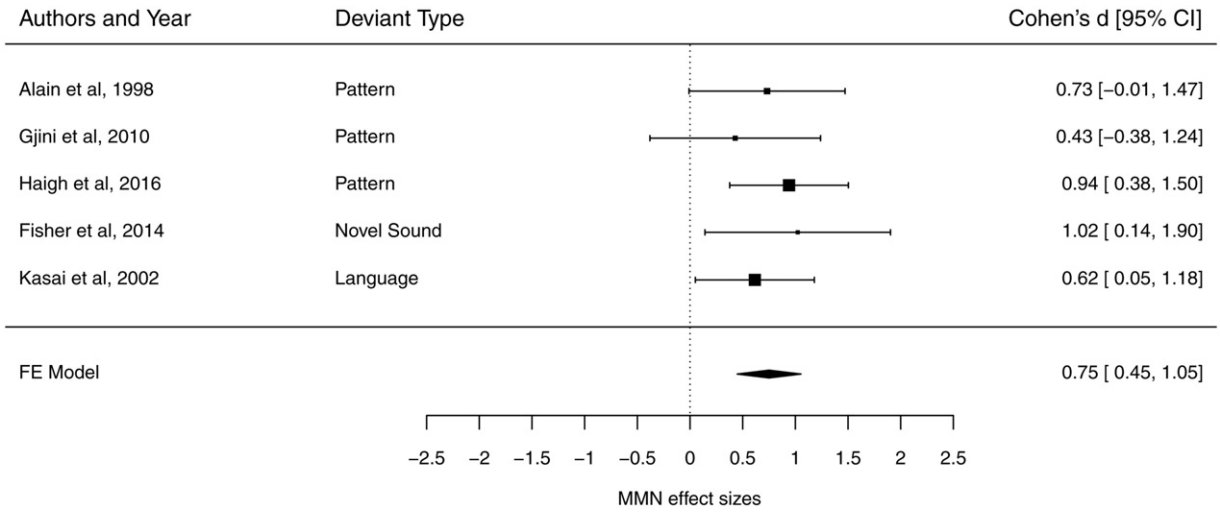

Fig. 3. MMN deficits in SCZ using complex abstract/pattern deviants. Effect sizes for individual HC vs SCZ samples are shown for studies using complex abstract/pattern deviants (as defined in Section 2.2) with 95% confidence intervals plotted as horizontal error bars. The pooled effect size using a fixed effects model is shown at the bottom including its 95% confidence interval. Positive values indicate lower MMN magnitudes in SCZ.

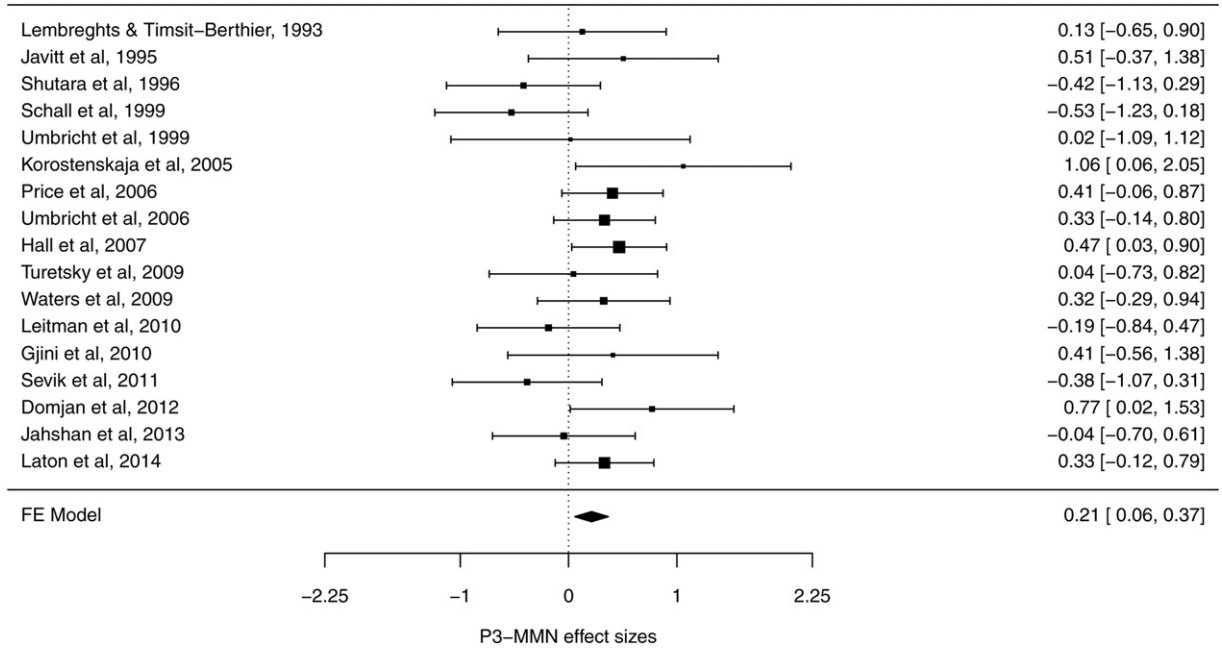

Fig. 4. A comparison of MMN and P3b deficits in SCZ. An effect size representing the difference in effect sizes for MMN and P3b in SCZ vs HC is shown for individual studies that measured both ERP components. 95% confidence are depicted as horizontal error bars. Exact values are reported on the right column including 95% confidence intervals in brackets. Positive values indicate greater deficits for SCZ in P3b than in MMN.

which MMN is maximally elicited in HC. It also may indicate that some of the differences observed between studies and deviant types could be due to the ability to detect MMN in HC.

Before accounting for the effect of MMN in HC, the effect of deviant type on this all-inclusive sample was statistically significant ($F_{4,179} = 3.283$, $p = 0.013$). However, following co-variation for normalized MMN amplitude in HC, the effect of deviant type was no longer significant ($F_{4,179} = 1.951$, $p = 0.104$). Similarly, an analysis of effect sizes to longer versus shorter duration deviants revealed significant differences prior to adjustment for the normalized MMN amplitude in HC ($F_{1,84} =$

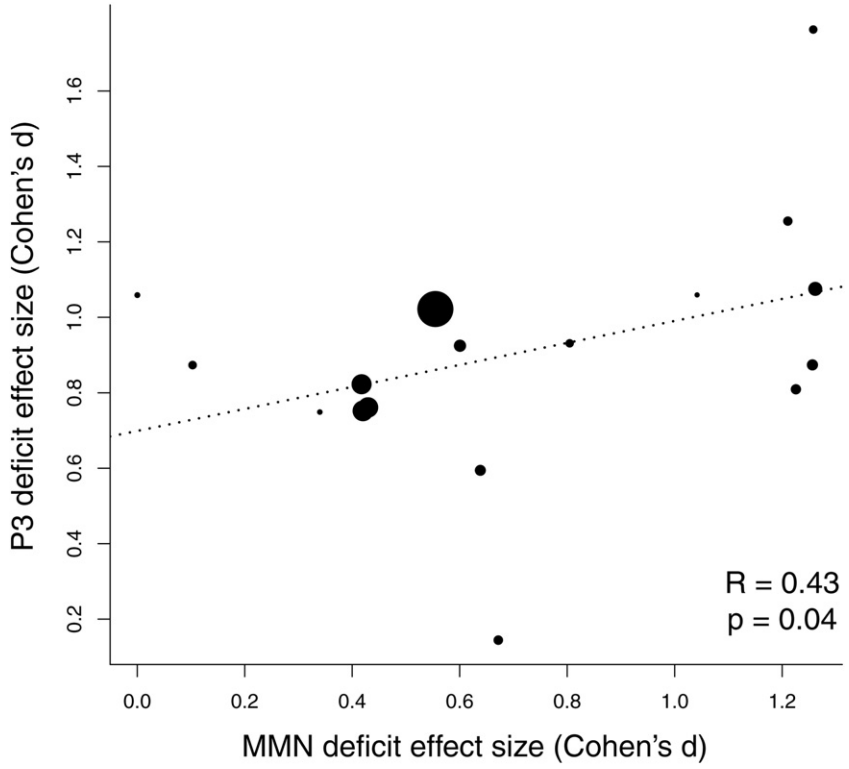

Fig. 5. P3b deficits correlate with MMN deficits in SCZ. The effect size of P3b deficits is plotted against the effect size of MMN deficits in each SCZ vs HC sample in which both components were measured. The dashed line represents the results of a correlation between the two variables computed from a weighted linear regression. Symbol sizes depict the weight given to each sample as determined by the variance estimate of MMN and P3b effect sizes. *R* is the correlation coefficient after adjusting for age and sex.

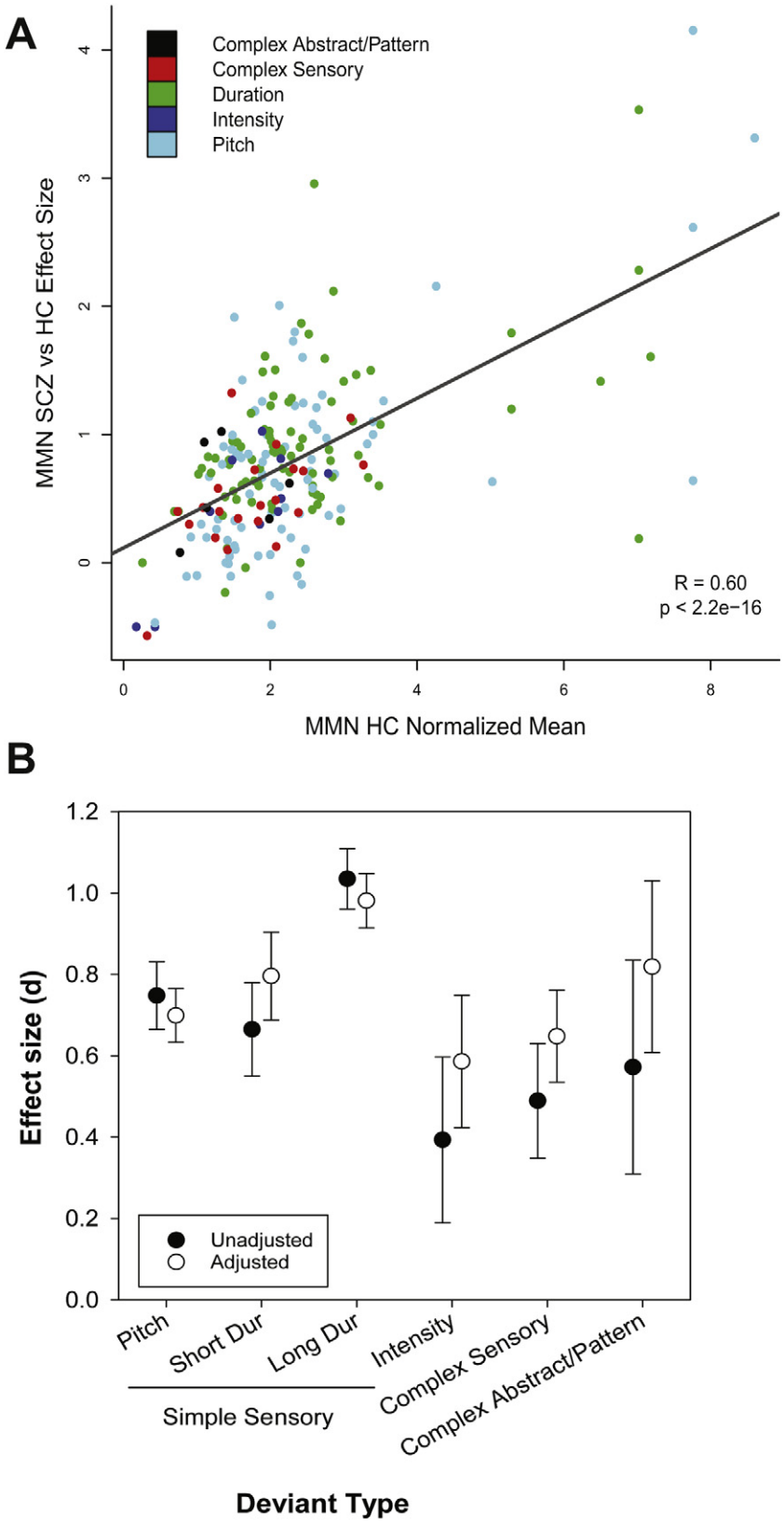

Fig. 6. The relationship between MMN deficits in SCZ and MMN magnitude in HC. (A) The effect size for SCZ vs HC sample comparison is plotted against the normalized mean of MMN in HC. Symbol colors denote the different deviant type categories (see key). The solid line is an unweighted linear regression. (B) Unweighted means for the effect sizes shown in A by deviant type as filled circles (duration also shown as longer and shorter duration separately). Empty circles represent the means adjusted for normalized amplitude of MMN in HC and error bars represent SD.

7.311, $p = 0.008$). This difference also lost significance following co-variation for normalized MMN amplitude in HC ($F_{1,83} = 2.049$, $p = 0.156$). Fig. 6B displays adjusted and unadjusted mean effect sizes (unweighted and pooled across all available study samples and conditions). The increase in uniformity when accounting for MMN in HC between deviant types appears driven by increases in effect size for intensity and more complex deviants.

In an additional analysis, we grouped simple (pitch, intensity, and duration) and complex (abstract/pattern and complex sensory) deviants together. A univariate ANOVA with complex versus simple deviant as the factor revealed that effect size was larger using simple deviants than complex deviants (unadjusted means 0.82 ± 0.69 versus 0.51 ± 0.38; $F_{1,182} = 5.40$, $p = 0.029$). After co-varying for MMN in HC, the difference in effect size between simple and complex deviants lost significance ($F_{1,181} = 0.911$, $p = 0.341$). The results suggest that the difference in effect sizes observed between simple and complex deviants is largely driven by the ability of each deviant type to elicit MMN in HC.

4. Discussion

4.1. The case for keeping it simple

Mismatch negativity has long shown promise as a biomarker for predicting conversion to, diagnosing, "bio-typing", "staging", individualizing treatment for, and tracking response to treatment of schizophrenia (Javitt and Freedman, 2015; Javitt and Sweet, 2015; Light and Swerdlow, 2015). Given the broad range of deviant types that can elicit MMN, questions remain as to which paradigm makes the "best" biomarker or whether different deviant types could serve disparate functions in the evaluation and management of the disorder. Related to this question is the continued exploration of the neural mechanisms underlying MMN deficits and what those mechanisms may say about the etiology and pathophysiology of schizophrenia (see Section 4.3). The current meta-analysis explores some of the conditions under which MMN deficits can be elicited and to our knowledge is the first to pool data from studies using complex deviants in SCZ.

One of our major findings is that MMN generation to complex deviants is significantly reduced in SCZ, parallel to observations with simple physical deviants. Moreover, reductions are observed both to complex sensory deviants, such as double deviants, gaps or omissions and to conceptual deviants, such as change in pattern or repeating stimuli. Nevertheless, the magnitude of deficit is no larger than the magnitude of deficit observed to simple sensory features (Figs. 1-3). These findings thus suggest that use of more complex deviants may be useful for testing specific neuroscientific hypotheses, but do not necessarily assist further in differentiation of schizophrenia spectrum disorders from healthy controls. These findings also argue that deviance detection mechanisms are likely uniformly impaired throughout the brain, potentially involving subcortical as well as cortical mechanisms (Lee et al., 2017) with each paradigm type likely emphasizing deviance detection at different stages in the auditory pathway.

In unadjusted analyses, MMN elicited by complex patterns showed a lesser degree of impairment than MMN elicited in more standard paradigms (Fig. 6). Nevertheless, these paradigms also tend to elicit relatively "noisy" MMN components even in healthy controls. Following adjustment for MMN signal-to-noise, MMN deficits to pattern deviants in SCZ were no longer reduced compared to MMN deficits to simple frequency or duration deviants.

4.2. Automatic vs. controlled processing

Schizophrenia is marked by several deficits along the auditory processing chain characterized by separate components of the auditory ERP. The current meta-analysis focused on MMN, a long-latency automatic component that reflects pre-attentive novelty detection. To our knowledge, we are the first to pool together studies that also examined an even later component, P3b, in the same patient samples, which reflects a later processing step involving controlled attention. This within-study approach was especially important in trying to understand the relationship between these two measures in the same samples and to better evaluate their relative deficits.

We found that while P3b deficits are larger than MMN deficits, this was only a small effect size difference between the two sets of measures, whereas the MMN deficit itself was in the range of moderate to large (0.5–0.8 SD). It is tempting to think of MMN as reflective of a processing step necessary to generate P3b, as both depend on successful discrimination between standards and deviants. If this were completely true, we would conclude that most of the deficit in P3b reflects dysfunction in an earlier pre-attentive processing step represented by MMN (based on their relative effect sizes reported in Section 3.3, MMN would account for 75% of the deficit).

However, the generation of P3b is more complex and likely involves other sensory, memory, and attentional processes not captured by MMN (Polich, 2007). In fact, when we examined the within-sample correlation between P3b and MMN (Fig. 5), we found that only 18.7% of the variance in P3b deficits could be accounted for by MMN deficits across studies, and some of this variance may reflect correlations due to study design rather than individual subject differences.

Therefore, P3b and MMN deficits likely represent separate dysfunctions in auditory processing that share some common mechanisms, with MMN deficit contributing to a small portion of P3b deficits. The estimate of the MMN's contribution is lower, however, than in a previous study in which structural equation modeling in the same sample of patients demonstrated that MMN accounted for about 50% of P3b deficit (Leitman et al., 2010). Our underestimate may be due to being unable to examine within-subject correlations directly. Overall, therefore, these findings suggest that not all of cognitive dysfunction in SCZ may be attributable to sensory dysfunction alone, and that deficits in additional higher order regions, such as frontal and parietal cortices (presumed generators of P3b) may contribute as well. At the same time, they support significant MMN contributions to P3b deficits, consistent with distributed hierarchical models (Leitman et al., 2010; Krishnan et al., 2009).

4.3. Neural mechanisms underlying MMN dysfunction in SCZ

On a cellular and micro-circuit level, MMN deficits in SCZ have been indirectly linked to NMDA receptor and GABA interneuron dysfunction (Javitt et al., 2000a, 2000b; Javitt and Sweet, 2015; Lavoie et al., 2008; Michie et al., 2016), also supported by more direct neuropharmacology evidence using NMDA-R antagonists in animals and healthy controls (Javitt et al., 1996; Umbricht et al., 2002, 2000). On a brain network level, it is still unclear how much of MMN deficit is due to bottom-up sensory discrimination deficits at the auditory cortex level or below versus higher-order top-down processing deficits. Micro-circuit and NMDA receptor dysfunction could be involved in either type of deficit and probably contribute to broad cortical dysfunction, consistent with disrupted network connectivity in SCZ.

The current meta-analysis does not directly probe the potential neural mechanisms underlying MMN deficits. That being said, we can infer that bottom-up sensory processes must play a significant role in explaining MMN deficits. First, there appears to be no difference in effect sizes between studies using simple versus complex deviants, and in fact simple deviants may offer an advantage in detecting robust deficits. Therefore, much of the dysfunction could lie in lower order processing localized to sensory areas of cortex or subcortical regions. This is also supported by our finding that P3b deficits are only modestly elevated compared to MMN deficits. Since P3b is representative of later stage attention and task relevancy dependent processing whereas MMN is known to be pre-attentive and largely generated in sensory regions, it is likely that bottom-up automatic sensory errors contribute to auditory pathway dysfunction reflected in late ERP components.

It has been argued that MMN deficits in SCZ must be due to higher order processing dysfunction since lower sensory impairments would be expected to generate more deficit as deviants become smaller and harder to detect (Erickson et al., 2016). However, it is known that healthy controls generate smaller MMN to lower deviance levels (e.g. May et al., 1999) and our results demonstrate that it is harder to detect group differences when MMN is smaller in HC (Fig. 6). This suggests that MMN deficits in SCZ would appear smaller at lower deviance levels which has been demonstrated in studies using within-subject designs (Horton et al., 2011; Javitt et al., 1998). This effect would occur regardless of the relative contribution of sensory and cognitive deficits to MMN reduction in SCZ.

4.4. Conclusions

MMN impairments in schizophrenia can be detected effectively using simple deviant oddball paradigms without the need for more complex rule violations. Moreover, in general, based on this meta-analysis, it appears that MMN deficits elicited by simpler deviant types are as large or larger than those observed in more complex paradigms. Furthermore, differences in MMN deficit effect size between deviant types is eliminated when accounting for the signal-to-noise of MMN in HC. Lastly, P3b, which reflects higher order task-dependent auditory processing is only modestly more impaired than MMN in SCZ.

The most current framework for understanding MMN generation is the predictive coding account, which allows both early sensory memory and higher order model adjustments to modulate MMN amplitude (Garrido et al., 2009). The results of this meta-analysis argue that sensory processing deficits play a significant role in lower MMN amplitudes in SCZ. There continue to be major unknowns regarding MMN deficits in SCZ, including how current psychological-level models (e.g. predictive coding) map onto underlying neural structures such as somatostatin interneurons or local circuit interactions (Javitt and Sweet, 2015; Lee et al., 2017). The present studies suggest that these can be adequately tested using simple deviant types, such as pitch or duration, that are most readily translated to animal models, and most easily probed at the intracortical level.

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Conflicts of interest

Dr. Javitt reports having received consulting payments within the last 36 months from Sunovion, Forum, and Takeda. He has received research support from Roche. He holds intellectual property rights for use of NMDA modulators in treatment of neuropsychiatric disorders. He holds equity in Glytech, AASI, and NeuroRX, and serves on the advisory board of Promentis and NeuroRx. All other co-authors report no conflicts.

Contributors

MA designed the study, collected the data, performed some of the basic analysis, and wrote the first draft of the manuscript. SX and YW were responsible for the majority of the statistical analyses and meta-analytic techniques. BV helped with the analysis, figure creation/preparation, and tables. JLC helped edit the manuscript and advised on technical details related to ERPs. DCJ contributed to all portions of study design, analysis, and writing and served as a supervisor and mentor on all aspects of the project. All authors contributed to and have approved the final manuscript.

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References

Berkey, C.S., Hoaglin, D.C., Mosteller, F., Colditz, G.A., 1995. A random-effects regression model for meta-analysis. Stat. Med. 14 (4), 395–411.
Chen, C., Liu, C.-C., Weng, P.-Y., Cheng, Y., 2016. Mismatch negativity to threatening voices associated with positive symptoms in schizophrenia. Front. Hum. Neurosci. 10, 362.
Erickson, M.A., Ruffle, A., Gold, J.M., 2016. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. Biol. Psychiatry 79 (12), 980–987.
Escera, C., Malmierca, M.S., 2014. The auditory novelty system: an attempt to integrate human and animal research. Psychophysiology 51 (2), 111–123.
Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009. The mismatch negativity: a review of underlying mechanisms. Clin. Neurophysiol. 120 (3), 453–463.
Haigh, S.M., Coffman, B.A., Murphy, T.K., Butera, C.D., Salisbury, D.F., 2016. Abnormal auditory pattern perception in schizophrenia. Schizophr. Res. 176 (2), 473–479.
Hay, R.A., Roach, B.J., Srihari, V.H., Woods, S.W., Ford, J.M., Mathalon, D.H., 2015. Equivalent mismatch negativity deficits across deviant types in early illness schizophrenia-spectrum patients. Biol. Psychol. 105, 130–137.
Hedges, L.V., Olkin, I., 1985. Statistical methods for meta-analysis. Phytochemistry 72 (13), 369.
Horton, J., Millar, A., Labelle, A., Knott, V.J., 2011. MMN responsivity to manipulations of frequency and duration deviants in chronic, clozapine-treated schizophrenia patients. Schizophr. Res. 126 (1), 202–211.
van Houwelingen, H.C., Arends, L.R., Stijnen, T., 2002. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat. Med. 21 (4), 589–624.
Javitt, D.C., Sweet, R.A., 2015. Auditory dysfunction in schizophrenia: integrating clinical and basic features. Nat. Rev. Neurosci. 16 (9), 535–550.
Javitt, D.C., Doneshka, P., Zylberman, I., Ritter, W., Vaughan, H.G., 1993. Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. Biol. Psychiatry 33 (7), 513–519.
Javitt, D.C., Doneshka, P., Grochowski, S., Ritter, W., 1995. Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. Arch. Gen. Psychiatry 52 (7), 550–558.
Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1996. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 93 (21), 11962–11967.
Javitt, D.C., Grochowski, S., Shelley, A.-M., Ritter, W., 1998. Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. Electroencephalogr. Clin. Neurophysiol. Potentials Sect. 108 (2), 143–153.
Javitt, D.C., Shelley, A.M., Silipo, G., Lieberman, J.A., 2000a. Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. Arch. Gen. Psychiatry 57 (12), 1131–1137.
Javitt, D.C., Shelley, A.M., Ritter, W., 2000b. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. Clin. Neurophysiol. 111 (10), 1733–1737.
Javitt, D.C., Freedman, R., 2015. Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. Am. J. Psychiatry 172, 17–31.
Jeon, Y., Polich, J., 2003. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40 (5), 684–701.
Kane, N.M., Curry, S.H., Butler, S.R., Cummins, B.H., 1993. Electrophysiological indicator of awakening from coma. Lancet 341 (8846), 688–689.
Kantrowitz, J.T., Hoptman, M.J., Leitman, D.I., Moreno-Ortega, M., Lehrfeld, J.M., Dias, E., Sehatpour, P., Laukka, P., Silipo, G., Javitt, D.C., 2015. Neural substrates of auditory emotion recognition deficits in schizophrenia. J. Neurosci. 35 (44), 14909–14921.
Krishnan, R.R., Keefe, R., Kraus, M., 2009. Schizophrenia is a disorder of higher order hierarchical processing. Med. Hypotheses 72 (6), 740–744.
Laton, J., Van Schependom, J., Gielen, J., Decoster, J., Moons, T., De Keyser, J., De Hert, M., Nagels, G., 2014. Single-subject classification of schizophrenia patients based on a combination of oddball and mismatch evoked potential paradigms. J. Neurol. Sci. 347 (1), 262–267.
Lavoie, S., Murray, M.M., Deppen, P., Knyazeva, M., Berk, M., Boulat, O., Bovet, P., Bush, A.I., Conus, P., Copolov, D., Fornari, E., Meuli, R., Solida, A., Vianin, C., Bucliln, T., Do, K.Q., 2008. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33 (9), 2187–2199.
Lee, M., Sehatpour, P., Hoptman, M.J., Lakatos, P., Dias, E.C., Kantrowitz, J.T., Martinez, A.M., Javitt, D.C., 2017. Neural mechanisms of mismatch negativity dysfunction in schizophrenia. Mol. Psychiatry 00:1–9. http://dx.doi.org/10.1038/mp.2017.3.
Leitman, D.I., Sehatpour, P., Higgins, B.A., Foxe, J.J., Silipo, G., Javitt, D.C., 2010. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. Am. J. Psychiatry 167 (7), 818–827.
Lembreghts, M., Timsit-Berthier, M., 1993. The value of cognitive psychophysiological studies in a comprehensive approach to schizophrenia (treatment of information and attention capacities in acute-stage schizophrenia). Acta Psychiatr. Belg. 93, 322–342 Spec No.
Li, Z., Zheng, B., Deng, W., Liu, X., Zheng, Z., Li, T., 2013. Multi-components of evoked-brain potentials in deficit and nondeficit schizophrenia. Asia-Pacific Psychiatry 5 (2), 69–79.
Light, G.A., Swerdlow, N.R., 2015. Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. Ann. N. Y. Acad. Sci. 1344 (1), 105–119.
Linden, D.E.J., 2005. The p300: where in the brain is it produced and what does it tell us? Neuroscientist 11 (6), 563–576.
May, P., Tiitinen, H., Ilmoniemi, R.J., Nyman, G., Taylor, J.G., Näätänen, R., 1999. Frequency change detection in human auditory cortex. J. Comput. Neurosci. 6 (2), 99–120.

Michie, P.T., Malmierca, M.S., Harms, L., Todd, J., 2016. The neurobiology of MMN and implications for schizophrenia. Biol. Psychol. 116, 90–97.
Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., Winkler, I., 2001. "primitive intelligence" in the auditory cortex. Trends Neurosci. 24 (5), 283–288.
Novak, G., Ritter, W., Vaughan, H.G., 1992. Mismatch detection and the latency of temporal judgments. Psychophysiology 29 (4), 398–411.
Perlman, G., Foti, D., Jackson, F., Kotov, R., Constantino, E., Hajcak, G., 2015. Clinical significance of auditory target P300 subcomponents in psychosis: differential diagnosis, symptom profiles, and course. Schizophr. Res. 165 (2), 145–151.
Perrin, M.A., Kantrowitz, J.T., Silipo, G., Dias, E., Jabado, O., Javitt, D.C., 2018. Mismatch negativity (MMN) to spatial deviants and behavioral spatial discrimination ability in the etiology of auditory verbal hallucinations and thought disorder in schizophrenia. Schizophr. Res. 191, 140–147.
Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118 (10), 2128–2148.
Raudenbush, S.W., 2009. Analzying Effect Sizes: Random-Effects Models. In: Cooper, H., Hedges, L.V., Valentine, J.C. (Eds.), The Handbook of Research Synthesis and Meta-Analysis. Russell Sage Foundation, New York, pp. 295–315.
Recasens, M., Grimm, S., Capilla, A., Nowak, R., Escera, C., 2012. Two sequential processes of change detection in hierarchically ordered areas of the human auditory cortex. Cereb. Cortex 24 (1), 143–153.
Rudolph, E.D., Ells, E.M.L., Campbell, D.J., Abriel, S.C., Tibbo, P.G., Salisbury, D.F., Fisher, D.J., 2015. Finding the missing-stimulus mismatch negativity (MMN) in early psychosis: altered MMN to violations of an auditory gestalt. Schizophr. Res. 166 (1), 158–163.
Salisbury, D.F., McCathern, A.G., 2016. Abnormal complex auditory pattern analysis in schizophrenia reflected in an absent missing stimulus mismatch negativity. Brain Topogr. 29 (6), 867–874.
Sallinen, M., Kaartinen, J., Lyytinen, H., 1994. Is the appearance of mismatch negativity during stage 2 sleep related to the elicitation of K-complex? Electroencephalogr. Clin. Neurophysiol. 91 (2), 140–148.
Schaefer, J., Giangrande, E., Weinberger, D.R., Dickinson, D., 2013. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr. Res. 150 (1), 42–50.
Shelley, A.M., Ward, P.B., Catts, S.V., Michie, P.T., Andrews, S., McConaghy, N., 1991. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. Biol. Psychiatry 30 (10), 1059–1062.
Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr. Res. 76 (1), 1–23.
Umbricht, D., Schmid, L., Koller, R., Vollenweider, F.X., Hell, D., Javitt, D.C., 2000. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. 57 (12), 1139–1147.
Umbricht, D., Koller, R., Vollenweider, F.X., Schmid, L., 2002. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. Biol. Psychiatry 51 (5), 400–406.
Umbricht, D.S.G., Bates, J.A., Lieberman, J.A., Kane, J.M., Javitt, D.C., 2006. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. Biol. Psychiatry 59 (8), 762–772.
Viechtbauer, W., 2010. Metafor: Meta-Analysis Package for R. R Package, Version 1.4–0.