A Meta-analytic Review of Auditory Event-Related Potential Components as Endophenotypes for Schizophrenia: Perspectives From First-Degree Relatives

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Introduction: As endophenotypes bridge the gap between genetics and phenotypic disease expression, identifying reliable markers is important for fostering understanding of pathophysiology. The present aim was to conduct current meta-analyses of 3 key auditory event-related potential (ERP) components that have been held as potential endophenotypes for schizophrenia: P50, P300 amplitude and latency, and mismatch negativity (MMN), reflective of sensory gating, attention and classification speed, and perceptual discrimination ability, respectively. In order to assess endophenotype viability, these components were examined in unaffected relatives of patients with schizophrenia and healthy controls. Methods: Effect sizes (ES) were examined between relatives and controls for P50 suppression (10 studies, n = 360 relatives, 473 controls), P300 amplitude (20 studies, n = 868 relatives, 961 controls), P300 latency (17 studies, n = 674 relatives, 792 controls), and MMN (11 studies, n = 377 relatives, 552 controls). Results: Reliable differences in P50 suppression (ES = 0.86, P < .001), P300 amplitude (ES = −0.52, P < .001), and P300 latency (ES = 0.44, P < .05) were found between unaffected relatives and controls. A trend was found between relatives and controls for MMN (ES = 0.21, P = 0.06), and the use of extraneous channels was found to be a significant moderator (P = 0.01). When MMN was analyzed using frontocentral channel Fz, a significant difference was found (ES = 0.26, P < 0.01). Discussion: The results indicate that P50 suppression, P300 amplitude and P300 latency, and MMN may serve as viable endophenotypes for schizophrenia.

Key words: schizophrenia/endophenotype/auditory ERP/relatives

Schizophrenia is a complex disease that involves a combination of numerous genetic and environmental factors.¹ Overt illness expression involves the interaction of many of these genotypic and environmental influences, thereby posing severe challenges to genetic dissection of the disease. An endophenotype is defined as an internal phenotype² that is discoverable using biochemical or microscopic tests.³ Endophenotypes form the causal links between genetic influences and overt phenotypic expression and are therefore key in the understanding of the underlying biological mechanisms of disease risk and expression. Unlike biological markers, which may not be heritable, criteria for an endophenotype include heritability of the marker as well as a higher prevalence of the marker in non-affected family members relative to the general population.⁴ The current study examines 3 potential neurophysiological endophenotypes of schizophrenia by systematically comparing unaffected relatives of patients with schizophrenia and healthy controls.

The strategy for validating endophenotypes for schizophrenia first involves identifying deficits in patients, followed by exploring evidence of heritability in unaffected relatives.³ It has been consistently demonstrated that patients with schizophrenia exhibit deficits in sensory and cognitive processing.⁵,⁶ Many studies have aimed to further explore these deficits using electroencephalography (EEG) to measure event-related potentials (ERPs). Three specific components, the P50, P300, and mismatch negativity (MMN) have been shown to reliably differ between patients with schizophrenia and healthy controls in response to auditory stimuli (Footnotes can be seen in Supplementary material). Example waveforms are shown in figure 1.

The P50 ERP component is a positive deflection occurring approximately 50 ms after stimulus onset and generally shows a decrease in amplitude to repeated stimuli, termed P50 suppression. Specifically, when two identical stimuli (eg, an auditory click) are presented successively, a decrease in P50 amplitude to the second stimulus is generally found. Many studies have demonstrated robust deficits in P50 suppression, as reflected by larger P50 ratios.
Auditory ERPs as Endophenotypes for patients with schizophrenia relative to healthy controls, which have been confirmed by meta-analytic studies. There is some debate of the functional significance of P50 suppression deficits. It may reflect increased EEG background noise in overall measurement, or in measuring the response to S2 due to refractory effects, but is most commonly posited to reflect a sensory gating mechanism or filtering of redundant stimuli. Indeed, some studies have shown P50 suppression deficits in patients with schizophrenia to be related to phenomenological dimensions of sensory gating. For example, the P50 ratio is found to be correlated with perceived invasiveness of sounds and scores on the Sensory Gating Inventory (SGI) in patients with schizophrenia (but see also Jin and coworkers), suggesting that P50 suppression deficits may indeed be indicative of an inability to inhibit the response to superfluous stimuli.

The P300 component is a positive deflection occurring between 250 and 500 ms after stimulus onset and is thought to reflect attentional processes. This component is often recorded using an oddball paradigm, in which the subject is presented with frequent and infrequent stimuli and asked to respond to the infrequent stimuli. An increase in amplitude to the infrequent relative to the frequent stimuli is generally found. As this increase in amplitude to the infrequent target is task dependent (ie, only occurs if the target is meaningful/the participant is asked to respond to the target), this component reflects

![Fig. 1. Example component waveforms. (A) Example auditory-evoked response from a healthy control (left) and patient with schizophrenia (right). Arrows mark the location of the P50 wave for the conditioning stimulus and identical test stimulus. T/C indicates the test-to-conditioning ratio for each subject. The P50 response to the second stimulus is attenuated for the healthy control subject, but not for patient with schizophrenia. (B) Grand average waveforms for 38 healthy control subjects (top) and 52 patients with schizophrenia (bottom) in response to an infrequent auditory stimulus to which participants made a button press. As marked by arrows, patients with schizophrenia exhibit smaller P300 amplitudes than healthy controls. (C) Grand average MMN response to an auditory pitch-deviant stimulus for 20 healthy control subjects (top) and 19 patients with schizophrenia (bottom). As marked by arrows, patients with schizophrenia exhibit smaller MMN amplitudes than healthy controls. All example waveforms were adopted and reprinted with permission from Turetsky et al. MMN = mismatch negativity.](https://academic.oup.com/schizophreniabulletin/article-abstract/42/6/1504/2399394)
the engagement of attention or context updating. It has been demonstrated that P300 amplitude is related to the amount of attentional resources devoted to the task, whereas P300 latency indexes stimulus classification speed. Findings of deficient P300 amplitude and latency for patients with schizophrenia relative to healthy controls are robust. Although the P300 can be studied using visual stimuli, it is the auditory modality that is most commonly studied in schizophrenia, given that this modality has demonstrated the strongest effects, has greater genetic influence, and reflects a vulnerability trait marker for schizophrenia.

Also recorded using an oddball paradigm is the MMN component that occurs in response to deviant stimuli. This response is elicited by auditory tones differing in a variety of perceptual features, such as frequency or duration. The MMN generally occurs 150–250 ms after the onset of the deviant stimulus, is maximal over frontocentral scalp locations, and is related to the degree of deviance. Unlike the P300, the MMN is elicited even in the absence of attention. The MMN reflects automatic auditory processing, perceptual discrimination ability, and sensory memory. Deficits in MMN generation are robust in patients with schizophrenia.

The P50, P300, and MMN Components as Potential Endophenotypes

Examining auditory ERP components in unaffected relatives of patients with schizophrenia offers many benefits beyond studies in patients alone. First, many of these components may be affected by confounds, such as medication usage, which can be problematic when studying patient groups. Additionally, by definition, an endophenotype must be present at a higher rate in unaffected family members relative to the general population. Assessing these potential endophenotypes within unaffected relatives is an important and necessary step in evaluating the viability of these markers as endophenotypes and therefore gaining a better understanding of the underlying genetics of schizophrenia.

The viability of neurophysiological endophenotypes of schizophrenia, including P50 suppression, P300, and MMN, were reviewed in 2007 by Turetsky and colleagues and have been examined in meta-analyses comparing relatives of patients with healthy controls. Also in 2007, de Wilde and colleagues conducted a small meta-analysis of P50 suppression involving six family studies. The results show a moderate-to-large effect size (ES = 0.85), demonstrating evidence for deficits in P50 suppression in relatives of patients with schizophrenia compared with the healthy controls. Additionally, in a meta-analysis involving 11 studies from 1983 to 2003, Bramon and colleagues found that P300 amplitude was significantly reduced (ES = 0.61) and latency was significantly longer (ES = 0.50) in relatives compared with the controls. Finally, a recent meta-analysis examined MMN impairment across patients with schizophrenia, high-risk individuals, and relatives of patients with schizophrenia. Eight studies of relatives were included and found a nonsignificant trend for relatives to exhibit reduced MMN amplitude compared with the controls (ES = 0.26, P = 0.053).

Current Study

The aim of the current study is to provide a comprehensive, up-to-date review, and meta-analysis of the potential of multiple ERP components, known to reflect different stages of processing of auditory stimuli and serve as endophenotypes for schizophrenia. Importantly, the current analyses include 3 additional studies of the P50 component, and 3 additional studies of the MMN relative to the most recent aforementioned meta-analyses. Furthermore, as it was not their primary analysis, the recent meta-analysis of the MMN did not examine potential moderating variables in relatives. To address this gap and assess these important potential endophenotypes, we have examined three ERP components, the P50, P300, and MMN, and potential moderating variables in unaffected relatives of patients with schizophrenia compared with the healthy controls.

Methods

Eligibility Criteria

Inclusion criteria for the current analyses were as follows: (1) the study included a sample of unaffected relatives of patients with schizophrenia and a healthy control group, (2) EEG was recorded in response to auditory stimuli, (3) at least one of the ERP components of interest (P50, P300, and MMN) was measured, (4) statistics were reported that allowed for calculation of the component of interest for both the relative and the control group, and (5) the article was written in English and published in a peer-reviewed journal. The cutoff date for the literature search was December 1, 2015.

Study Selection

The literature search was conducted using Google Scholar with the following search terms: Schiz* AND P50/P300/Mismatch Negativity/MMN AND Relatives OR Family. The resulting articles were checked for eligibility, and the citations were cross-referenced. For the P50, 10 studies met eligibility criteria (n = 360 relatives, 473 controls). For P300, 23 studies met eligibility criteria. In order to prevent biased estimates, 2 studies were excluded from the analysis because subjects participated in another study were used in the current analyses. In these cases, the most recent study was used for the current analysis. Of the remaining 21...
studies, 20 (n = 868 relatives, 961 controls) examined and reported P300 amplitude and 17 (n = 674 relatives, 792 controls) examined and reported P300 latency. For MMN, 11 studies met eligibility criteria and were used in the analyses (n = 377 relatives, 552 controls).

Analyses
The variables of interest were P50 suppression, P300 latency, P300 amplitude, and MMN of relatives compared with the healthy controls in response to auditory stimuli. P50 suppression was defined in each study as the ratio of S2:S1 amplitude at the vertex (Cz) within a specified time window ranging from 40 ms to 80 ms after stimulus onset, where S1 is the first, or conditioning, stimulus and S2 is the second, or testing, stimulus. Therefore, a larger ratio is indicative of less suppression. The P50 methods (eg, 500 ms interstimulus interval between paired clicks) and analyses (eg, recorded at channel Cz) were highly consistent between studies. Due to the low number of studies and high consistency between them, no potential moderating variables were analyzed.

The P300 component was defined in each study as a positive deflection generated by the target (infrequent) tones within a specific time window generally ranging from 200 ms to 600 ms poststimulus onset. For both the P300 amplitude and latency, most studies reported 3 midline sites (Fz, Cz, and Pz). Therefore, when reported separately, amplitude and latency were averaged across channels for each condition. The channels and time windows used in each study are reported in Table 1. Differential P300 amplitude has been shown based on gender, age, and response (eg, button press or silent counting), making these important moderating variables to consider.

MMN was measured in each study bysubtracting the averaged amplitude in response to the deviant stimuli from the averaged amplitude in response to the standard stimuli within a specified time window ranging from 50 ms to 250 ms poststimulus onset, with a larger negative number indicating greater MMN. This is typically measured at frontocentral channels, however, some studies have reported MMN as averaged across parietal and/or occipital channels. As patients with schizophrenia typically show the largest MMN deficits at fronto-central channels, the inclusion of extraneous (non-frontal) channels for MMN calculation is included as a moderating variable in the current analyses. Other factors that have been shown to impact the MMN are age and whether frequency or duration deviants are measured. Hence, channel location, relative age, and task (frequency or duration) are all examined as potential moderating variables.

For each study, pooled ES (Hedges' g) was calculated to define the differences in these ERP components for the relative and control groups. Hedges' g was defined as the difference between group variables divided by pooled within-group SD of both groups. The standardized ES were analyzed using random effects meta-analyses that assumes random variability beyond sampling error. The funnel plot method was used to assess publication bias or the increased probability of statistically significant results to be published. An asymmetrical funnel plot and significant Egger's regression test of asymmetry suggests publication bias due to negative studies with smaller sample sizes not appearing in the literature.

Results
P50: The mean weighted ES of the 10 studies was of large magnitude (ES = 0.86, SE = .21, 95% CI: 0.44, 1.27), with suppression of relatives being smaller than that of healthy controls. This weighted mean ES differed significantly from zero (z = 4.04, P < .001). The forest plot is shown in Figure 2. This distribution of the ES indicated heterogeneity (Qe = 45.54, P < .001), therefore the dispersion of ES is greater than expected from sampling error. The funnel plot was symmetrical and Egger's regression test of funnel plot asymmetry was not significant (z = 1.36, P = .17).

P300 Amplitude
The mean weighted ES of the 20 studies was of medium magnitude (ES = −0.52, SE = .15, 95% CI: −0.82, −0.23), with amplitude of relatives being smaller than that of healthy controls (see Figure 3). This weighted mean ES differed significantly from zero (z = −3.52, P < .001). This distribution of the ES indicated heterogeneity (Qe = 91.70, P = .001), therefore the dispersion of ES is greater than expected from sampling error. The funnel plot was asymmetrical and Egger's regression test of funnel plot asymmetry was significant (z = −4.32, P < .001). The following moderating variables were tested using a mixed effects model: (1) the ratio of males to females in the relative sample, (2) the average age of relatives, and (3) the response required of participants. Results indicate that ratio (P = .43), relative age (P = .15), and no response (P = .38) were significant moderators. These moderators did not account for significant heterogeneity in ES, (Qe = 90.12, P < .001).

P300 Latency
The mean weighted ES of the 17 studies was of small- to medium magnitude (ES = 0.44, SE = .20, 95% CI: 0.04, 0.84), with latency of relatives being longer than that of healthy controls (see Figure 3). This weighted mean ES differed significantly from zero (z = 2.17, P < .05). This distribution of the ES indicated heterogeneity (Qe = 178.96, P < .001), therefore the dispersion of ES
Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Relative Sample</th>
<th>Relative Psychiatric Disorders (n)</th>
<th>Channel(s)</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>P50</td>
<td></td>
<td></td>
<td>SZ (1, moved to clinical group in study), Remitted MDD (5), Current MDD (6)</td>
<td>Cz</td>
<td>40–80 ms</td>
</tr>
<tr>
<td>Clementz et al</td>
<td>1998</td>
<td>First-degree</td>
<td>No mood disorder, any psychotic symptom, or a substance abuse diagnosis</td>
<td>Cz</td>
<td>40–80 ms</td>
</tr>
<tr>
<td>de Wilde et al</td>
<td>2007</td>
<td>Siblings</td>
<td>No lifetime diagnosis of psychotic disorder, BD, or SZ spectrum PD</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Hall et al</td>
<td>2007</td>
<td>MZ twins</td>
<td>None (107), BD (13), unspecified functional psychosis (3), schizoaffective disorder (1), MDD (11), minor depressive disorder (6), GAD (3), panic disorder (2), alcoholism (2), alcoholism with schizotypal features (1), minor depression with schizotypal features (2)</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Louchart-de la Chapelle et al</td>
<td>2005</td>
<td>Parents</td>
<td>Schizotypal PD (8)</td>
<td>Cz</td>
<td>40–80 ms</td>
</tr>
<tr>
<td>Mykes-Worsley</td>
<td>2002</td>
<td>Parents and siblings</td>
<td>Diagnosis of SZ were excluded</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Siegel et al</td>
<td>2004</td>
<td>First-degree</td>
<td>Diagnosis of SZ were excluded</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Turetsky et al</td>
<td>2012</td>
<td>First-degree</td>
<td>No history of psychiatric problems</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Waldo et al</td>
<td>1988</td>
<td>First-degree</td>
<td>BD excluded</td>
<td>Cz to left mastoid, Cz to right mastoid, Cz to Oz</td>
<td>NR</td>
</tr>
<tr>
<td>Blackwood et al</td>
<td>1991</td>
<td>Relatives up to 3 generations</td>
<td>None (107), BD (13), unspecified functional psychosis (3), schizoaffective disorder (1), MDD (11), minor depressive disorder (6), GAD (3), panic disorder (2), alcoholism (2), alcoholism with schizotypal features (1), minor depression with schizotypal features (2)</td>
<td>Cz</td>
<td>40–75 ms</td>
</tr>
<tr>
<td>Bramon et al</td>
<td>2008</td>
<td>First-degree</td>
<td>Nonpsychotic</td>
<td>Pz (amplitude) Fz, Pz (latency)</td>
<td>NR</td>
</tr>
<tr>
<td>Bramon et al</td>
<td>2005</td>
<td>First-degree</td>
<td>Nonpsychotic</td>
<td>Pz, Fz, Cz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>de Wilde et al</td>
<td>2008</td>
<td>Siblings</td>
<td>No history of mood disorder, any psychotic symptom or substance abuse</td>
<td>Pz, Fz, Cz</td>
<td>250–450 ms</td>
</tr>
<tr>
<td>Dutt et al</td>
<td>2012</td>
<td>First-degree</td>
<td>No illness (59), MDD (13), GAD (1), panic disorder (1)</td>
<td>Pz, Fz, Cz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Franguo et al</td>
<td>1997</td>
<td>First-degree</td>
<td>No illness (47), Remitted Depression (8), Remitted BD (1), Remitted Bulimia Nervosa (1)</td>
<td>Pz, Fz, Cz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Hall et al</td>
<td>2007</td>
<td>MZ twins</td>
<td>Remitted MDD (5)</td>
<td>Pz</td>
<td>280–600 ms</td>
</tr>
<tr>
<td>Karoumi et al</td>
<td>2000</td>
<td>Siblings</td>
<td>No Axis I disorder</td>
<td>Pz, Fz, Cz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Kidogami et al</td>
<td>1991</td>
<td>Parents and siblings</td>
<td>No history of psychiatric disorders</td>
<td>Pz, Fz, Cz</td>
<td>260–460 ms</td>
</tr>
<tr>
<td>Kimble et al</td>
<td>1994</td>
<td>Children and siblings</td>
<td>No psychotropic medications</td>
<td>Pz, Fz, Cz, Oz</td>
<td>280–450 ms</td>
</tr>
<tr>
<td>Lebedeva and Orlova</td>
<td>2001</td>
<td>Children and siblings</td>
<td>Diagnosis of SZ were excluded</td>
<td>Pz</td>
<td>260–550 ms</td>
</tr>
<tr>
<td>Price et al</td>
<td>2006</td>
<td>First-degree</td>
<td>None (26), MDD (3), Minor Depressive Disorder (1)</td>
<td>Pz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Roxborough et al</td>
<td>1993</td>
<td>Relatives (degree NR)</td>
<td>None (51), Remitted MDD (13), GAD (1), panic disorder (1)</td>
<td>Pz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Schreiber et al</td>
<td>1992</td>
<td>Children</td>
<td>Drug free</td>
<td>Pz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Ševik et al</td>
<td>2011</td>
<td>Siblings</td>
<td>No Axis I disorder</td>
<td>Pz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Simons et al</td>
<td>2011</td>
<td>Siblings</td>
<td>Non-psychotic</td>
<td>Pz, Fz, Cz</td>
<td>280–500 ms</td>
</tr>
<tr>
<td>Turetsky</td>
<td>2000</td>
<td>Siblings</td>
<td>No Axis I disorder</td>
<td>Pz, Fz, Cz</td>
<td>280–400 ms</td>
</tr>
<tr>
<td>Weisbrod</td>
<td>1999</td>
<td>MZ twins</td>
<td>None (4), remitted BD (2), single depressive episode (2)</td>
<td>Pz</td>
<td>270–470 ms</td>
</tr>
<tr>
<td>Winterer et al</td>
<td>2003</td>
<td>Siblings</td>
<td>No history of psychotic illness, Present but clinically stable depression or PD (14), History but not current nonpsychotic disorder (39)</td>
<td>F3, F4, T5, T6</td>
<td>260–420 ms</td>
</tr>
</tbody>
</table>
Auditory ERPs as Endophenotypes

The funnel plot was asymmetrical and Egger’s regression test of funnel plot asymmetry was not significant ($z = 0.62$, $P = .54$). Moderating variables were again tested using a mixed effects model, which showed that the male to female ratio ($P = .61$), relative age ($P = .51$), and no response ($P = .39$) were significant moderators and that these moderators did not account for significant heterogeneity in ES ($QE_{13} = 135.39$, $P < .001$).

Mismatch Negativity

The mean weighted ES of the 11 studies was of small magnitude ($ES = 0.21$, $SE = .11$, 95% CI: $-0.01$, 0.42). Although there was a trend, this weighted mean ES did
not differ significantly from zero ($z = 1.90, P = .06$). This distribution of the ES indicated heterogeneity ($Q_{10} = 18.57, P = .05$), therefore the dispersion of ES is greater than expected from sampling error. The funnel plot was symmetrical and Egger’s regression test of funnel plot asymmetry was not significant ($z = 1.16, P = .25$).

The following moderating variables were tested using a mixed effects model: (1) the average age of relatives, (2) whether the reported amplitudes included additional channels (eg, Oz) outside of the frontal channels, and (3) whether MMN was calculated based on a duration or frequency deviation task. The results showed that neither age ($P = .63$) nor task ($P = .36$) were significant moderators. There was, however, a significant effect of reported channels ($z = -2.47, P = .01$). The moderating variables accounted for the previously found significant heterogeneity in ES ($Q_{E} = 9.10, P = .25$).
Auditory ERPs as Endophenotypes

In order to further explore whether MMN deficits are found in relatives of patients compared with the controls, an additional exploratory meta-analysis was conducted looking only at MMN amplitude in the Fz channel. Of the 11 studies provided sufficient data for ES calculation in Fz, the mean weighted ES of the 8 studies was again of small magnitude (ES = 0.26, SE = .08, 95% CI: 0.09, 0.42), however, this weighted mean ES differed significantly from zero (z = 3.02, P < .01). This distribution of the ES did not indicate heterogeneity (Q = 7.80, P = .35), therefore the dispersion of ES is not greater than expected from sampling error. The MMN forest plot is shown in in figure 4.

Discussion

An ideal neurophysiological endophenotype is one that exhibits a robust deficit in both patients with schizophrenia and unaffected family members, is easily measured with limited subject demands, and demonstrates high reliability. We have assessed whether 3 ERP components may fit these criteria by specifically examining whether these components, which are easily measured, demonstrate high reliability, show robust and stable deficits in the patient population (for a review, see Turetsky et al), and are also reliably deficient in unaffected relatives. The present study comprehensively reviewed all current literature examining 3 key ERP components assessing sensory and attentional processing of auditory stimuli: P50 suppression, P300, and MMN. The results suggest that deficits in these components may all be viable candidates for schizophrenia endophenotypes.

Twin and family studies have shown heritability in each of the components examined in the current review. For example, a twin study calculated heritability estimates of 68% for P50 suppression, 63% for MMN peak amplitude, and 69% for P300 amplitude. In an intriguing study,
these 3 components were studied concomitantly within a sample of monozygotic and dizygotic twins in order to assess the genetic overlap between them. Interestingly, there was little evidence of a genetic association between these separate components, suggesting that they each may represent different cognitive processes that are influenced by independent sets of genes. Therefore, individuals who exhibit abnormalities in more than one of those components may carry a higher genetic loading. Studying all 3 of these components within high-risk populations would therefore offer greater power in determining susceptibility of phenotypic disease expression.

Patients with schizophrenia have been shown to have deficits in P50 suppression relative to healthy controls, thereby being potentially susceptible to sensory overload.\(^9\)\(^{10}\) The current analysis demonstrated that relatives of patients also exhibit this deficit relative to healthy controls, which is consistent with the heritability of P50 suppression that has been shown in genetic studies.\(^81\)\(^{83}\) The magnitude of the ES found in the current analysis (ES = 0.86) is large and replicates the previous smaller meta-analysis of this population (ES = 0.85\(^{10}\)). Although smaller, this ES is comparable to the large ES magnitude for patients with schizophrenia relative to healthy controls (eg, ES = 1.28\(^{10}\)). Thus, P50 suppression meets heritability criteria needed to serve as an endophenotype. Furthermore, P50 suppression is measured without the need of an explicit response from the participant. Although there are potential disadvantages, such as excessive boredom and potential for subjects to fall asleep, the lack of subject demands may make the P50 an ideal neurophysiological endophenotype for schizophrenia.

The P300 component is an exogenous component that is involved in the engagement of attention, processing of novelty, and context updating to changes in the environment.\(^84\) Patients with schizophrenia have been shown to exhibit deficits in both P300 amplitude and latency.\(^9\)\(^{23}\) The current study has demonstrated reliable differences in P300 amplitude and latency between unaffected relatives of patients and healthy controls, suggesting deficits in attention and novelty processing (amplitude) as well as perceptual processing speed (latency) in unaffected relatives. The ES values in the current analysis (amplitude ES = 0.52; latency ES = 0.44) were marginally smaller than those previously shown in a meta-analytic review of the P300 in schizophrenia (amplitude ES = 0.85; latency ES = 0.57\(^9\)) and previously reported for relatives (amplitude ES = 0.61; latency ES = 0.50\(^9\)). Furthermore, we did not find male-to-female ratio, relative age, or response required by participants to have a significant influence on the ES or to explain the heterogeneity found. The reliable deficits found in the current study suggest that P300 deviations are a premorbid marker of risk, irrespective of subject demands and are not dependent on the phenotypic expression of the disease.

In the primary analysis, it was shown that although there was a trend, no reliable difference between MMN was found between relatives and healthy controls. This is in stark contrast to the large magnitude of the ES for differences in MMN between patients with schizophrenia and healthy controls (ES = 0.99\(^9\)) and is consistent with the results of a recent meta-analysis of relatives (ES = 0.26\(^9\)). However, the use of extraneous channels was shown to be a significant moderating variable and accounted for a great deal of heterogeneity. Interestingly, differences in scalp topography of the MMN in patients with schizophrenia relative to healthy controls have been shown with impairment in frontal but not temporal regions in patients.\(^74\)\(^{76}\) Indeed, there is evidence that two distinct neural generators underlie the MMN, superior temporal generators and frontal generators.\(^86\)\(^{87}\) as evidenced by current source density maps\(^88\)\(^{89}\) and equivalent current dipole modeling.\(^90\) Although still an area of debate, it has been posited that upon detection of a stimulus change in the temporal circuits, the frontal generator is used for involuntary attention switching.\(^91\) When only the results reported for channel Fz were examined, a significant deficit in MMN amplitude was found for relatives. This may be a result of increased noise when irrelevant posterior channels are included or may be indicative of deficits in the frontal MMN subcomponent. It has been suggested that MMN deficits are related to disease progression or imminent conversion to psychosis rather than genetic vulnerability to the disease.\(^29\)\(^{32}\) Indeed, MMN reduction has also been shown to predict conversion to psychosis in clinical high-risk individuals,\(^32\)\(^{92}\)\(^{93}\) and a previous meta-analysis of the MMN in schizophrenia found a systematic increase in ES as a function of illness duration.\(^29\)\(^{29}\) However, a more recent meta-regression between patients and healthy controls failed to find significant linear relationship between illness duration and ES, suggesting that progressive impairment is not a linear process.\(^92\) Additional research on the MMN in unaffected relatives of patients with schizophrenia is warranted.

The current analysis may have implications for both the genetic associations underlying the phenotypical expression of schizophrenia and the cognitive functioning of those at risk of the disease. The concept of a multilayered information processing system has been posited,\(^92\) and it has been suggested that although separate, these layers may overlap to some extent.\(^96\) P50 suppression and MMN are thought to be pre-attentional processes involved in sensory “gating out” of irrelevant sensory input and “gating in” of important information, respectively.\(^97\) Successful stimulus encoding involves both these processes, and the processed stimuli are then evaluated,\(^21\) and environmental changes are updated,\(^98\) as indexed by P300 latency and amplitude. The lack of inter-component heritability of these measures,\(^82\) as well as varying deficits of these measures in unaffected relatives, suggests distinct underlying genetic influences of these cognitive processes. Our results
suggest both attentional deficits and deficient inhibition of irrelevant auditory input in unaffected relatives. It remains possible that only some relatives exhibit one or more of these deficits. Indeed, bimodal distributions have been found in independent studies of unaffected relatives for the P300 and for P50 suppression. The phenotypic expression of schizophrenia may involve a combination of these deficits. Studies of individual differences in these components in both patients and relatives would inform the genetic underpinnings of schizophrenia and may guide the development of specific drugs and therapies for treatment. For example, P50 suppression deficits have been associated with the alpha-7 nicotinic receptor gene. Therefore, alpha-7 agonists may be feasible treatments for auditory sensory gating impairments in schizophrenia.

Conclusion
The systematic examination of potential endophenotypes is a critical step in understanding underlying genetic influences of the disease. Here, we have identified 3 auditory ERP components that meet the criteria for endophenotypes of schizophrenia. The results of these meta-analyses suggest that relatives of patients with schizophrenia reliably demonstrate deficits in sensory gating, attentional processing, stimulus classification, and perceptual discrimination ability, as indexed by P50 suppression, P300 amplitude, P300 latency, and MMN, respectively.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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