Reductions in the N1 and P2 Auditory Event-Related Potentials in First-Hospitalized and Chronic Schizophrenia

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The N1 auditory event-related potential (ERP) is reduced in chronic schizophrenia, as is the P2 to attended tones. N1 reduction may be endophenotypic for schizophrenia, being reduced in twins of schizophrenic patients and showing heritability. Results in family members, however, are equivocal, with abnormally small N1 (consistent with an endophenotype) and abnormally large N1 (inconsistent with an endophenotype) reported. P2 has been little studied in schizophrenia or family members. One crucial step in establishing endophenotypes is to rule out causal chronicity factors. We examined schizophrenia patients within 1 year of first hospitalization (most within 2 wk), chronically ill patients, and matched controls to examine N1 and P2 reductions and disease stage. Two active target detection oddball tasks were used, one with 97-dB tones against 70-dB white masking noise, the second with 97-dB tones without noise. Results from 8 samples are reported: first-hospitalized patients and matched controls and chronic patients and matched controls for the 2 tasks. N1 and P2 were measured from the standard stimuli. N1 and P2 were significantly reduced in chronic patients, as expected, and reduced in first-hospitalized patients. Because N1 and P2 are reduced even at the first hospitalization for schizophrenia, they may serve as viable electrophysiological endophenotypes for the disorder. However, deficit early in the disease is necessary but not sufficient to establish these ERPs as endophenotypes. Deficits must next be demonstrated in at least a subset of unaffected family members, a crucial criterion for an endophenotype.

Key words: schizophrenia/first episode/event-related potential/endophenotype/N1/N100/P2/P200

Introduction

The auditory evoked potential (AEP) includes short-latency (brain stem), mid-latency (thalamic and cortical), and long-latency (cortical) responses. The long-latency potentials of the AEP comprise the N1 (N100) and P2 (P200) peaks, the so-called vertex potentials. These potentials are known to be tightly coupled to stimulus parameters; eg, their latency is decreased and their amplitude increased as sound intensity is increased. This has led to their classification as exogenous or sensory potentials. The vertex potentials do not represent the first volley of sensory information into the primary auditory cortex, which occurs on the order of tens of milliseconds rather than hundreds. In addition, the vertex potentials represent several components with different brain generators,1 some of which are not purely sensory but are modulated by subjective mental operations. For example, attention to the tones can lead to an increase in the amplitudes of N1 and P2 and hence there is some endogenous aspect to the vertex potentials, eg, O’Donnell et al.2 Thus, the N1 and P2 are probably best considered event-related potentials (ERPs) encompassing both exogenous and endogenous potentials.

Much research has examined the N1 to various auditory stimulus configurations in schizophrenia. The N1 elicited to standard tones on a relatively slow oddball ERP task (standard and target tones presented every 1–2 s) is reduced in chronic schizophrenia.3–5 This reduction is present regardless of whether the subjects attended to all stimuli and counted the rare tones or ignored the tones and read a book2 or simply did a passive task6 and so cannot reflect reduction in only the endogenous component of N1. Kayser et al7 reported reduced N1 to both complex tones and phonemes in schizophrenia. Using binaural single-tone AEP tasks, Saletu et al8 showed that N1 was reduced in all schizophrenia patients whether characterized by thought disorder or more negative symptoms. Kessler and Steinberg,9 however, argued that N1 reductions were present in paranoid but not undifferentiated or residual schizophrenia, although their samples were relatively small (9 residual/undifferentiated patients vs 9 controls). Adler et al10 showed reduced AEP N1 amplitudes at 1-s interstimulus intervals (ISIs) in schizophrenia. Connolly et al11 showed reductions of

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N1 in schizophrenia using monaural stimuli. Boutros et al.\textsuperscript{12} reported reduced N1 amplitude (and increased latency) in schizophrenia to the first of 2 clicks presented in a gating task.

Javitt and colleagues focused on the effects of ISI on N1 amplitude. Shelly et al.\textsuperscript{13} showed that schizophrenia patients showed increasing N1 abnormalities at longer ISIs. Javitt et al.\textsuperscript{14} found in monkeys that N1 and P2 had different refractoriness periods for various ISIs as in humans\textsuperscript{3,15} and that phencyclidine (PCP) reduced the vertex potentials only at long ISIs. As suggested by Javitt, the N1 deficits may only occur in at long ISIs in schizophrenia, in line with the monkey PCP data above, reflecting deficit in a process that is selectively activated at long ISIs and relies on N-methyl-D-aspartate channel. Such a pattern may also reflect a ceiling effect at longer ISIs where controls continue to recruit nonrefractory processing neurons (the N1 gets quite large at longer ISIs), but schizophrenia patients have recruited all available resources due to reductions of auditory cortex gray matter. This differential ISI effect may explain why some studies see no reduction of N1 at shorter ISIs, eg, Umbricht et al.\textsuperscript{16} see Javitt.\textsuperscript{17} Paradoxically, using extremely long ISIs (>12 s), Roth et al.\textsuperscript{18} reported reduced N1 in medicated schizophrenia patients but not in unmedicated patients. Clearly, there have been relatively few examinations of ISI effects on N1 in schizophrenia, and the results have been contradictory.

The issue of whether medication, rather than disease pathology, causes N1 reductions has been the subject of many investigations. The results have been equivocal. Pfefferbaum et al.\textsuperscript{19} showed no reduced N1 in off-medication patients in an oddball task, but Ogura et al.\textsuperscript{20} showed reduced N1 in off-medication patients. Connolly et al.\textsuperscript{21} showed smaller “N120” in unmedicated patients (minimum 6-wk washout) using dichotic stimuli. Within single-tone auditory evoked potential (AEP) tasks, Buchsbaum’s review\textsuperscript{22} indicated that medications did further reduce N1, though also noting negative findings. Adler et al.\textsuperscript{23} reported no differences in N1 between medicated and unmedicated schizophrenia. Roemer and Shagass\textsuperscript{24} claimed medication reduced visual but not overall auditory N1 amplitudes in patients. Boutros et al.\textsuperscript{25} reported smaller P2 amplitude in schizophrenia to the first of 2 clicks presented in a gating task. O’Donnell et al.\textsuperscript{26} reported reduced P2 in chronic schizophrenia but not in bipolar disorder. Karoumi et al.\textsuperscript{27} reported no reductions in P2 amplitude in chronically ill schizophrenia (ChSz) and their well siblings vs controls, although patients and siblings were generally one-third to one-half SD smaller than controls. Siblings showed longer peak latency P2 at Cz only.

If N1 and P2 are reduced in schizophrenia and are associated with some of the genetic risk factors for schizophrenia as suggested by the extant literature, then it is important for the ERPs to be reduced at the first hospitalization for schizophrenia rather than to develop with disease course. Only 2 articles report on N1 in schizophrenia at first episode, with conflicting results, and only one of those articles reported P2. Brown et al.\textsuperscript{28} used a relatively specific method of averaging N1 to standards (50-ms pips, 1.3-s ISI, 60-dB SPL) preceding vs following a target stimulus on an auditory oddball task in 40 first-episode schizophrenia patients, 40 patients chronically ill with schizophrenia, and matched controls. They found reduced N1 to standards before and after targets (and to targets) in first-episode schizophrenia, just like in chronically ill patients. By contrast, however, Valkonen-Korhonen et al.\textsuperscript{29} reported no N1 reductions in 25 first psychosis subjects to monaural (right ear) stimuli on an auditory oddball task (pips duration not specified, 1.0-s ISI, 55-dB nHL). Inspection of figure 1 from that article shows larger N1 in first-hospitalized psychosis patients than in matched controls. Caveats to the study include the fact that the psychotic patients studied were diagnostically mixed, with only 13/25 subjects meeting criteria for schizophrenia or schizophrreniform disorder, and inclusion of unipolar (3) and bipolar (1) affective disordered subjects, and the fact that N1 amplitude was collapsed across 58 sites for analysis. Brown et al.\textsuperscript{30} reported statistically
significant smaller P2 in first-hospitalized schizophrenia (FHSz) to standards after targets. The P2 to standards before targets was also smaller than in controls, but differences did not survive Bonferroni correction. To summarize, the evidence on N1 and P2 reductions in FHSz is scant and equivocal. Further, using the same number of trials to average standard and target ERPs, as in Brown et al., is essential when comparing responses to standard and target stimuli to equate the signal-to-noise ratio (33 trials maximum in that study). However, averaging all available standards, as in Valkonen-Korhonen et al., gives the best estimate of the true ERP with the least noise. It is not essential to examine target effects to determine if N1 and P2 are reduced in FHSz, and using all standard trials will provide a more accurate estimate of the true ERPs.

The present study examined whether N1 and P2 deficits were present in patients first hospitalized, or within 1 year of first hospitalization, for schizophrenia or schizophreniform disorders vs age-, parental socioeconomic status-, handedness-, gender-, and Wechsler Adult Intelligence Scale—Revised/Third Edition information subtest scaled score–matched controls. In addition, chronic schizophrenia patients and appropriately matched controls were tested to establish the pattern of deficits in clearly documented psychiatrically ill subjects. Two different paradigms were performed on 2 separate groups of samples as well, resulting in 2 groups of FHSz subjects and 2 groups of younger controls and 2 groups of chronically ill patients and 2 groups of older controls. Although examination of task parameter effects on N1 and P2 was not the main reason for the different paradigms (see “Stimuli” below), 2 separate samples allow for immediate replication of findings and comparison of effects across different stimulus configurations. For N1 and P2 to serve as powerful endophenotypes, they must be obligatorily reduced in schizophrenia, even at the time of first hospitalization rather than a consequence of illness duration. This is the main measure of interest in this article.

Methods

Subjects

Subjects had no history of a learning disability, including dyslexia, special education, childhood treatment for attention deficit disorder/attention deficit/hyperactivity disorder, any infectious or neurological disease affecting the central nervous system, any loss of consciousness >20 minutes and/or traumatic brain injury with sequelae, electroconvulsive therapy, drug or alcohol detox or dependence within the last 5 years, intravenous drug abuse ever, or seizure disorder. Subjects had to have a minimum ninth-grade education and an estimated IQ > 85. Patients were recruited from May 1993 through September 2002 from consecutive inpatient admission at McLean Hospital, a private psychiatric facility affiliated with Harvard Medical School. FHSz patients were at their first hospitalization for psychosis or less than 1 year from their first inpatient admission for psychosis (n = 55). Unless FHSz patients refused medication, all were acutely medicated for therapeutic reasons. Patients were tested usually within 2 weeks of any lifetime exposure to antipsychotic medications. ChSz patients had multiple previous admissions for schizophrenia spanning more than 1 year from protocol

Fig. 1. Even-Related Potentials to Standard Tones in FHSz Vs Young Controls and ChSz Vs Older Controls. Panel A: responses to 97-dB standards with 70-dB background white noise. Panel B: responses to 97-dB standards with no noise. Note: FHSz: first-hospitalized schizophrenia, ChSz: chronically ill schizophrenia, Con: controls.
entrance (n = 56). Unless refusing medication, all ChSz patients were medicated at the time of testing and had received multiple courses of pharmacologic treatment in their lifetimes. All patients received a research diagnosis based on the SCID P interview and chart review. (Approximately 50% of the FHSz subjects received follow-up diagnoses. For exhaustive details regarding subject recruitment and diagnosis, please see Salisbury et al.)

Control subjects were recruited from newspaper advertisements in the greater Boston area and were screened using the SCID NP and SCID II. No control subject had an Axis I psychiatric disorder in a first-degree relative by report. All subjects had normal hearing as assessed with audiometry, defined as within 30-dB nHL, no more than 15-dB difference between ears at 500, 1000, and 1500 Hz. The method of ascending limits was used in 5-dB steps (begin at 0 nHL, down 1 step, up 2, down 1, up 2, etc, until detection, then down 3, repeat procedure until 3 hits at a specific intensity).

During the 9.5 years during which data were recorded, 2 auditory oddball tasks were presented, with no overlap between subjects receiving each task. Paradigms changed when the stimulus delivery systems were upgraded. Tasks are described in detail below ('Stimuli' section), but briefly, subjects detected low-probability target tones from among more frequently presented standard tones (the ubiquitous auditory oddball task). For the purposes of this study, N1 and P2, the vertex potentials, were measured from the response to standard stimuli. This avoids contamination with target detection–related brain processes (eg, mismatch negativity [MMN], N2, P3) and provides a high signal-to-noise ratio due to the great number of trials.

Electroencephalogram Recording
Electroencephalogram (EEG) activity was recorded from the scalp through 28 tin electrodes in preconfigured caps (ElectroCap International, Eaton, OH) using Neuroscience amplifiers and Neuroscan Acquire software. Electrode sites included all 10–20 sites excluding T1/2 and Oz; FTC1/2; TCP1/2, PO1/2; and CP1/2. Ground horizontal eye movements (bipolar recording). Electrodes placed at the outer canthi of the eyes were used to monitor vertical eye movements and blinks (bipolar recording). All electrode impedances were below 3 kΩ, and the ears were matched within 1 kΩ. The EEG amplifier band-pass was 0.15 (6 dB per octave roll-off) to 40 Hz (36 dB per octave roll-off). Single-trial epochs were digitized at 3.9 milliseconds per sample over 900 milliseconds, including a 100-millisecond prestimulus baseline. Averaging and artifact rejection were done off-line using BrainVision Analyzer.

ERP responses were convolved with a zero phase-shift digital low-pass filter at 20 Hz with a 24 dB per octave roll-off to remove ambient electrical noise, muscle artifact, and other high-frequency signals. Within each 200-trial block, epochs from each electrode site were baseline corrected by subtraction of the average prestimulus voltage and corrected for eye movement artifact using the method of Gratton et al. After eye correction, baseline correction was once again performed. Subsequently, epochs that contained voltage exceeding ±50 μV at F7, F8, Fp1, or Fp2 were rejected. Averages were computed for the brain responses to standard tones, which contain little to no N2 and P3 activity. Peak N1 amplitude was automatically detected as the most negative point from 50 to 200 milliseconds at the vertex (Cz) and adjusted if necessary after visual inspection. Peak P2 amplitude was automatically detected as the most positive point from 150 to 300 milliseconds at the vertex (Cz) and adjusted if necessary after visual inspection. Voltages from all sites were based on Cz peak latency. N1 and P2 amplitudes were quantified by the mean voltage over 3 digital bins (peak ± 1 bin, 11.7 ms).

Stimuli
From May 1993 through January 1998, stimuli were generated using a Neuroscience stimulator. Subjects silently counted binaurally presented target tones (97-dB SPL, 1.5-kHz tones, 50-ms duration, 10-ms rise/fall, 15% of trials) among standard tones (97 dB, 1 kHz) against a background of 70-dB white noise mask for extraneous room sounds. There were 200 tones presented in total, 170 standards and 30 targets. Tones were presented every 1.2 seconds. Thirty-two FHSz subjects (6 females, mean age 29.1 ± 8.0 y, 1 left-handed, illness and medication information in table 1) and 32 matched controls (6 females, mean age 26.5 ± 7.2 y, 1 left-handed) and 45 ChSz patients (all males, mean age 36.7 ± 6.7 y, all right-handed, illness and medication information in table 1) and 34 matched controls (all males, mean age 33.3 ± 9.2 y, all right-handed) were compared using these stimuli (97-dB tones with background white noise).

From February 1998 through September 2002, stimuli were generated using Neuroscan STIM software. Subjects silently counted binaurally presented target tones (97-dB SPL, 1.5-kHz tones, 50-ms duration, 10-ms rise/fall, 15% of trials) among standard tones (97 dB, 1 kHz). There was no background white noise, which this version of STIM was unable to generate. There were 200 tones presented in total, 170 standards and 30 targets. Tones were presented every 1.2 s. Twenty-three FHSz subjects (4 females, mean age 23.7 ± 5.7 y, 2 left-handed, illness and medication information in table 1) and 23 matched controls (5 females, mean age 23.7 ± 4.5 y, 1 left-handed) and 11 ChSz patients (all males, mean age 38.1 ± 8.5 y, all right-handed, illness and medication information in table 1) and 19 matched controls (all males, mean age 37.7 ± 9.0 y, all right-handed) were
compared using these stimuli (97-dB tones in the absence of background white noise).

**Analyses**

Statistics were performed using SPSS. Demographic variables were compared for matching using t tests. N1 and P2 latencies at Cz were analyzed using an omnibus univariate analysis of variance (ANOVA) with group (schizophrenia vs control), chronicity/age (FHSz, younger controls vs ChSz, older controls), and task (stimuli with vs without background noise) as between-group factors. The sum of the squares used type III and the model corrected for the intercept. For amplitudes, an omnibus repeated-measures ANOVA was performed that included all between-subjects factors with the addition of the within-subjects factor site (Fz, Cz, Pz). Huynh-Feldt epsilon was used to adjust the df for the site factor. Omnibus ANOVAs included 55 FHSz, 55 younger controls, 56 ChSz, and 53 older controls. One hundred eleven schizophrenic patients were compared with 108 controls, 110 first-hospitalized younger subjects were compared with 109 chronically ill older subjects, and 143 subjects performed the oddball task with white noise, 76 without white noise. Follow-up ANOVAs were planned to decompose interactions in the omnibus ANOVAs that involved the task and chronicity factors. Significance was attained at \( P < .05 \). Effect sizes are presented using partial \( \eta^2 \). To aid interpretation, partial \( \eta^2 \) can be converted to \( f \), the ANOVA equivalent of \( d \). When comparing 2 groups, \( f \) is equivalent to \( \sqrt{d} \). A small effect size of \( f = 0.1 \cong \) partial \( \eta^2 = 0.01 \), a medium effect size of \( f = 0.25 \cong \) partial \( \eta^2 = 0.06 \), and a large effect size of \( f = 0.4 \cong \) partial \( \eta^2 = 0.14 \).36

**Results**

ERP waveforms are presented in figure 1. Robust N1 and P2 potentials are evident.

Table 1. Clinical Information

<table>
<thead>
<tr>
<th></th>
<th>FHSz, With Mask</th>
<th>ChSz, With Mask</th>
<th>FHSz, Without Mask</th>
<th>ChSz, Without Mask</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS total</td>
<td>37.0 (9.9)</td>
<td>40.4 (8.3)</td>
<td>36.4 (13.2)</td>
<td>34.4 (9.0)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2.7 (1.8)</td>
<td>3.5 (2.2)</td>
<td>3.1 (1.9)</td>
<td>3.1 (1.5)</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>4.0 (2.2)</td>
<td>3.8 (1.9)</td>
<td>3.2 (2.2)</td>
<td>3.0 (1.7)</td>
</tr>
<tr>
<td>Unusual thought</td>
<td>4.3 (1.8)</td>
<td>4.9 (1.8)</td>
<td>2.0 (1.6)</td>
<td>1.8 (1.3)</td>
</tr>
<tr>
<td>Disorganization</td>
<td>2.2 (1.5)</td>
<td>3.5 (1.9)</td>
<td>2.1 (1.3)</td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td>Illness duration (y)</td>
<td>n/a</td>
<td>12.6 (6.8)</td>
<td>n/a</td>
<td>16.0 (9.3)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ equivalents</td>
<td>316.7 (363.5)</td>
<td>367.8 (293.4)</td>
<td>205.6 (151.5)</td>
<td>301.2 (207.9)</td>
</tr>
<tr>
<td>Unmedicated</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown/blind study</td>
<td>1</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Atypical antipsycotics</td>
<td>17b</td>
<td>14c</td>
<td>5d</td>
<td></td>
</tr>
<tr>
<td>Typical antipsycotics</td>
<td>14e</td>
<td>18f</td>
<td>1g</td>
<td>3h</td>
</tr>
<tr>
<td>Multiple antipsycotics</td>
<td>2i</td>
<td>7j</td>
<td>7k</td>
<td>2l</td>
</tr>
</tbody>
</table>

*Note: Values are mean (SD). FHSz, first-hospitalized schizophrenia; ChSz, chronically ill schizophrenia; BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine; n/a, not applicable.

• 2 Clozaril, 1 seroquel, 2 olanzapine, 6 risperidone.
• 10 Clozaril, 2 olanzapine, 5 risperidone.
• 2 Clozaril, 9 olanzapine, 3 risperidone.
• 1 Clozaril, 2 seroquel, 2 risperidone.
• 4 Haldol, 8 trilafon, 1 prolxin, 1 navane.
• 6 Haldol, 3 trilafon, 4 prolxin, 1 navane, 1 stelazine, 1 loxitan, 1 thoridazine, 1 mesoridazine.
• Trilafon.
• 1 Haldol, 2 trilafon.
• 1 Clozaril and stelazine, 1 haldol and trilafon.
• 1 Clozaril and thorazine, 2 clozaril and haldol, 1 olanzapine and haldol, 2 risperidone and prolxin, 1 olanzapine, risperidone, and thoridazine.
• 1 Seroquel and risperidone, 1 seroquel and olanzapine, 1 olanzapine and risperidone, 2 olanzapine and haldol, 1 olanzapine and trilafon, 1 risperidone and haldol.
• 1 Clozaril and trilafon, 1 seroquel and olanzapine.
Table 2. ERP Amplitudes to 97-dB Tones With 70-dB Background White Noise

<table>
<thead>
<tr>
<th>Group</th>
<th>Fz</th>
<th>Cz</th>
<th>Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHSz (n = 32)</td>
<td>-4.5 (2.5)</td>
<td>-4.3 (2.5)</td>
<td>-2.4 (1.9)</td>
</tr>
<tr>
<td>Younger controls (n = 32)</td>
<td>-5.0 (2.5)</td>
<td>-5.1 (2.8)</td>
<td>-3.0 (2.1)</td>
</tr>
<tr>
<td>ChSz (n = 45)</td>
<td>-3.9 (2.2)</td>
<td>-3.9 (2.2)</td>
<td>-2.2 (1.5)</td>
</tr>
<tr>
<td>Older controls (n = 34)</td>
<td>-5.1 (2.2)</td>
<td>-5.1 (2.1)</td>
<td>-2.8 (1.9)</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHSz (n = 32)</td>
<td>2.7 (2.6)</td>
<td>4.7 (3.0)</td>
<td>3.3 (2.6)</td>
</tr>
<tr>
<td>Younger controls (n = 32)</td>
<td>2.8 (2.5)</td>
<td>5.3 (2.9)</td>
<td>4.0 (2.2)</td>
</tr>
<tr>
<td>ChSz (n = 45)</td>
<td>2.5 (1.8)</td>
<td>4.1 (2.1)</td>
<td>2.8 (1.8)</td>
</tr>
<tr>
<td>Older controls (n = 34)</td>
<td>3.5 (2.1)</td>
<td>5.2 (2.0)</td>
<td>3.3 (1.7)</td>
</tr>
</tbody>
</table>

Note: Values are mean (SD) μV. ERP, event-related potential; FHSz, first-hospitalized schizophrenia; ChSz, chronically ill schizophrenia.

**N1 Latency**

N1 latency was not significantly different between schizophrenia (120.0 ± 10.9 ms) and control subjects (121.2 ± 12.0 ms, F_{1,211} = 1.0, P = .32, partial η² = 0.005). N1 latency was affected by the different stimulus parameters on the 2 tasks, with the presence of background noise significantly slowing N1 (123.6 ± 12.0 ms) relative to the absence of background noise (115.0 ± 11.3 ms, F_{1,211} = 28.42, P = .005, partial η² = 0.12). The main effects of chronicity/age and all interactions were nonsignificant, with partial η² between 0.0 and 0.004.

**N1 Amplitude**

The omnibus repeated-measures ANOVA revealed significantly smaller N1 in schizophrenia (−3.65 ± 2.25 μV) than in controls (−4.78 ± 2.46 μV, F_{1,211} = 14.01, P < .001, partial η² = 0.062, see table 2 for noncollapsed means). N1 was significantly smaller in the presence of background noise (−3.88 ± 2.21 μV) than in its absence (−4.81 ± 2.65 μV, F_{1,211} = 5.84, P = .017, partial η² = 0.027). N1 amplitude was larger at Fz and Cz than at Pz (F_{2,422} = 336.22, P < .001, ε = 0.80, partial η² = 0.61). However, N1 distribution differed between groups (F_{2,422} = 3.32, ε = 0.80, P = .048, partial η² = .015), largely due to less group difference at Pz than at Fz and Cz. There was a significant site by task interaction (F_{2,422} = 20.73, ε = 0.80, P < .001, partial η² = 0.089), again largely due to less modulation of N1 at Pz by perceived loudness (tones are perceived as louder without background noise). Finally, there was a 4-way interaction between group, chronicity/age, task, and site (F_{2,422} = 3.77, ε = 0.80, P = .033, partial η² = 0.018), reflecting relatively larger separation between ChSz and older controls at Pz without noise (see figure 1).

Although there was no effect of chronicity/age (F_{1,211} = 0.31, P = .58, partial η² = 0.001) and chronicity/age did not interact between patient groups (F_{1,211} = 0.63, P = .43, partial η² = 0.003) or between patient groups and stimulus (F_{1,211} = 0.06, P = .80, partial η² < 0.000), figure 1 suggests N1 differences with controls in FHSz may be smaller than in ChSz. Comparison of FHSz and younger controls revealed significant N1 reductions in FHSz (F_{1,106} = 4.33, P = .04, partial η² = 0.039). Comparison of ChSz and older controls revealed significant N1 reductions in ChSz (F_{1,105} = 10.86, P = .001, partial η² = 0.094). Thus, both groups are reduced in N1 amplitude, although the effect size is larger in chronic patients. Still, even with more than 200 subjects, statistical support for different degrees of reduction between FHSz and ChSz was not attained.

Because the different tasks affected N1 amplitude differently and interacted with topography, separate ANOVAs were performed for each task. In the presence of 70-dB background noise, N1 was smaller in schizophrenia (−3.32 ± 1.96 μV) than in controls (−4.30 ± 2.06 μV, F_{1,139} = 5.57, P = .02, partial η² = 0.039, see table 2 for noncollapsed means). N1 amplitude was larger at Fz and Cz than at Pz (F_{2,278} = 174.03, P < .001, ε = 0.74, partial η² = 0.56). No other main effects or interactions were significant, with partial η² between 0.0 and 0.009.

For stimuli presented without background noise, N1 was smaller in schizophrenia (−3.71 ± 2.49 μV) than in controls (−5.59 ± 2.36 μV, F_{1,72} = 7.49, P = .008, partial η² = 0.094, see table 2 for noncollapsed means). N1 amplitude was larger at Fz and Cz than at Pz (F_{2,144} = 146.43, P < .001, ε = 0.89, partial η² = 0.67). No other main effects or interactions were significant, with partial η² between 0.0 and 0.029.

**P2 Latency**

P2 latency was shorter in schizophrenia (217.3 ± 32.6 ms) than in controls (233.5 ± 32.0 ms, F_{1,211} = 13.27, P < .001, partial η² = 0.059). The presence of background white noise slowed P2 latency (232.44 ± 31.9 ms) relative to no noise (211.8 ± 31.6 ms, F_{1,211} = 25.50, P < .001, partial η² = 0.108). The main effects of chronicity/age and all interactions were nonsignificant, with partial η² between 0.0 and 0.006.

**P2 Amplitude**

The omnibus repeated-measures ANOVA revealed significantly smaller P2 in schizophrenia (3.48 ± 2.31 μV) than in controls (4.56 ± 2.79 μV, F_{1,211} = 9.32, P = .003, partial η² = 0.042, see table 3 for noncollapsed means). P2 was significantly smaller in the presence of background noise (3.63 ± 2.28 μV) than in its absence (4.74 ± 2.96 μV, F_{1,211} = 10.98, P = .001, partial η² = 0.049). P2 was larger at Cz than Fz and Pz (F_{2,422} = 198.04, P < .001, ε = 0.81, partial η² = 0.484). Of interest was an interaction between group, chronicity/age, and task (F_{1,211} = 17.84, P < .001, η² = 0.081, see table 3 for noncollapsed means).
schizophrenia. Partial correlation analysis was performed to assess the relationship between N1 and P2 amplitudes with clinical scores (Brief Psychiatric Rating Scale, BPRS, and Positive and Negative Syndrome Scale, PANSS) and medication dosages (chlorpromazine equivalents). The PANSS includes all BPRS items and was used to assess psychotic symptoms. The BPRS is a 24-item scale that assesses positive and negative symptoms, and the PANSS consists of 30 items evaluating general psychopathology (22), negative symptoms (7), and disorganization or secondary schizophrenia (1).

Table 3. ERP Amplitudes to 97-dB Tones Without Background White Noise

<table>
<thead>
<tr>
<th>Group</th>
<th>Fz</th>
<th>Cz</th>
<th>Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHSz (n = 23)</td>
<td>-5.0</td>
<td>-5.1</td>
<td>-2.3</td>
</tr>
<tr>
<td>Younger controls (n = 23)</td>
<td>-6.8</td>
<td>-6.7</td>
<td>-2.6</td>
</tr>
<tr>
<td>ChSz (n = 11)</td>
<td>-4.7</td>
<td>-4.8</td>
<td>-1.6</td>
</tr>
<tr>
<td>Older controls  (n = 19)</td>
<td>-6.4</td>
<td>-6.9</td>
<td>-3.5</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHSz (n = 23)</td>
<td>2.0</td>
<td>4.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Younger controls (n = 23)</td>
<td>2.4</td>
<td>7.8</td>
<td>5.6</td>
</tr>
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<td>ChSz (n = 11)</td>
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</tr>
<tr>
<td>Older controls  (n = 19)</td>
<td>4.4</td>
<td>7.4</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Note: Values are mean (SD) μV. ERP, event-related potential; FHSz, first-hospitalized schizophrenia; ChSz, chronically ill schizophrenia.

Because chronicity/age interacted with P2 topography, separate ANOVAs were performed for each matched age group. In FHSz and younger controls, P2 was smaller in schizophrenia (3.56 ± 2.48 μV) than in controls (4.56 ± 3.16 μV, F1,106 = 5.02, P = .027, partial η2 = 0.045, see table 2 for noncollapsed means). P2 amplitude was larger at Cz than at Fz and Pz (F2,210 = 84.21, P < .001, ε = 0.78, partial η2 = 0.445). There was an interaction between site and task in both groups, with more modulation of P2 amplitude without noise at Cz (F2,210 = 6.71, P = .004, ε = 0.78, partial η2 = 0.060). No other main effects or interactions were significant, with partial η2 between 0.0 and 0.015.

Clinical Scores and Medication

Symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) and later the Positive and Negative Syndrome Scale (PANSS). For uniformity, BPRS scores were “back engineered” from PANSS scores because the PANSS includes all BPRS items. There were no consistent associations between N1 and P2 amplitudes and clinical scores that were replicated in the second sample. There was an association between more impaired N1 amplitude elicited to tones with background noise and increased hallucinations in FHSz patients (r = 0.42), but this was not confirmed in the FHSz patients receiving tones in the absence of background noise, who, if anything, had larger N1s with increased hallucination scores (r = -0.47) or in either ChSz sample (r values ~ 2.0). Likewise, there was an association between larger P2 and greater BPRS total scores at Cz and Pz in the FHSz patients in the noise condition, but these associations were not replicated in the no-noise condition or in the ChSz samples.

Correlations of chlorpromazine equivalents for medications and N1 and P2 were performed separately for the tasks, collapsed across FHSz and ChSz. In the larger dataset (n = 74) for the stimuli with background noise, N1 latency was moderately lower in those patients with higher dosages and vice versa (r = 0.26, P = 0.2). Likewise, N1 was moderately smaller in those patients with higher dosages and vice versa (Cz, r = 0.29, P = 0.01; Pz, r = 0.34, P = 0.003). These moderate associations were not apparent in the group receiving tones in the absence of background noise (n = 34; latency, r = 0.06, not significant [NS]; amplitude, Cz, r = 0.17, NS; Pz, r = 0.11, NS). Using partial correlations on the entire sample (n = 108) adjusting for the main effects of stimuli and chronicity on ERPs revealed small but stable relationships between medication dosages and N1 latency (r = 0.22, P = 0.03) and amplitude (Fz, r = 0.21, P = 0.03; Cz, r = 0.24, P = 0.01; Pz, r = 0.26, P = 0.008). There were no associations between medication levels and P2 latency or amplitude for either task. Comparing those patients on atypical neuroleptics (n = 50) only vs those with classic neuroleptics or both (n = 49) revealed no significant effects on any N1 or P2 parameter. Comparing those patients only on atypicals (n = 50) vs those...
only on classic neuroleptics \((n = 35)\) revealed no effects of medication on any N1 or P2 parameter.

**Discussion**

The results show that N1 and P2 are reduced in schizophrenia, both in chronically ill patients and at the first hospitalization. The reductions in N1 occurred with no latency differences between groups and likely reflect abnormalities of the primary N1 generators in superior temporal gyrus auditory cortices. The finding of shorter P2 peak latencies and smaller amplitudes in ChSz and FHSz compared with their matched controls replicates the pattern observed by O’Donnell et al\(^2,5\) in chronically ill patients and are consistent with the absence of an endogenous, attention-related P2 component termed P2b. In well controls, this slightly later component overlaps the slightly earlier, more sensory P2 component(s), leading to a larger and later peak P2 amplitude.\(^2\) Because all schizophrenia samples in this study showed earlier P2 latencies and smaller amplitudes, we speculate that the reduction in P2 relates to reductions in P2b, a component responsible for P2 augmentation during attention to tones within a specific sensory channel. The results in first-episode schizophrenia are consistent with findings of Brown et al\(^29\) of reduced N1 and P2 to subsets of standards in FHSz. N1 and P2 reductions appear to be robust phenomena associated with schizophrenia. Their presence at first hospitalization suggest they may be suitable candidates for intermediate endophenotypes.

P2 is simply understudied in schizophrenia. We found reduced P2 with earlier peaks in all patient samples, consistent with the topography O’Donnell et al\(^2\) attributed to deficient P2b. The finding is in contrast, however, with the observation of later P2 latencies in relatives of schizophrenia patients.\(^28\) Definitive studies of N1 and P2 in relatives are necessary. If relatives do not show the same deficits observed in patients, then the utility of these ERPs as endophenotypes is questionable. Such studies are not only underway in several laboratories, but the N1 and P2 to frequent stimuli from the extant family studies that focused only on ERPs to the target stimuli (eg, P3) provide a large extent database for analysis that should be examined.

The lack of stable correlations with symptoms across both samples suggests that N1 and P2 amplitudes are little affected by the state of the subjects. Although N1 has been shown to be smaller during hallucinations, it does not appear to be smaller per se at all times in patients that hallucinate more than others. This in some way strengthens the argument for N1 and P2 as endophenotypes, as they seem more associated with the trait of being schizophrenic rather than the state of present symptom exacerbation.

Vertex potential reductions do not need to be pathognomonic for schizophrenia to be useful as endophenotypes. An endophenotype may well be expressed in the population but at relatively low frequency. Neither do all persons with schizophrenia need show a small N1 or small P2. Those who do, however, may have a certain genetic makeup as part of their entire constellation of genetic risk factors. N1 and P2 may serve as tools sensitive to the genetic risk factors. Other disorders may show N1 and P2 reductions. However, the path to such reductions is likely to be different in these diseases. Because N1 and P2, whatever their functional roles, are clearly in the information processing stream that is affected in schizophrenia, they are not simply epiphenomenal endophenotypes (as might be fingerprint whorls or hair swirls, eg) but rather are close to the functional pathway of impaired cognition in the disorder (namely, auditory processing, language, and thought).

There were moderate correlations between the dosage of medication and both N1 slowing and amplitude reduction. The effects sizes were rather small. There were no effects of medication classes in these relatively large samples. Thus, it seems unlikely that medications cause the initial N1 and P2 reductions, although medications appear to exert some modest effects on their timing and size. The following analysis was done to try to remove medication effects from the patient’s Cz N1 amplitudes. Because no control took antipsychotics and medication overlapped entirely with diagnosis, analysis of covariance or multivariate analysis of covariance cannot be used. Instead, the unstandardized B weight for medication dose within patients, after regressing for chronicity and stimuli, was used to adjust N1 amplitude according to the formula: adjusted\(_{Cz} = \text{raw\(_{Cz}\)} - (0.02 \times \text{meds}).\) Although this method has many assumptions and should be interpreted cautiously, N1 differences between groups remained \((P = .026),\) as did the main effect of stimulus \((P = .002).\) Although reassuring, it remains unclear what role medication levels play in AEP reductions or whether the amount of medications deemed clinically necessary and the degree of N1 and P2 abnormalities are consequences of some other primary abnormality.

Although the general pattern on N1 and P2b reductions were the same in ChSz and FHSz, there were some subtle differences. The effect size for difference with matched controls was larger in ChSz than in FHSz, although substantial subject Ns would be necessary to attain statistical significance for any chronicity-related effect. The absence of background noise, leading to a perceptually louder tone, led to less P2b augmentation in FHSz than in ChSz. Given that the ChSz sample sizes were relatively small for the task without noise, caution should be used in assessing this complex interaction. It is likely that both groups showed moderate N1 and P2 augmentation to the louder stimuli.

One interesting finding in this study was the difference in P2 topography between younger and older subjects.
Younger subjects, regardless of whether they were psychiatrically ill or well, showed markedly reduced frontal amplitude of P2. It is interesting to note that the age ranges between the “younger” and “older” samples were not that large. This effect seems to be a rather rapid change in the late 20s. This aging effect deserves further study to determine the underlying physiology and relation to brain maturation during the late third decade.

Several caveats need to be considered with regard to the data. We tested relatively few women, all in the first-hospitalized samples and younger controls. Thus, the degree to which these results generalize to women is not entirely clear. There are many factors that affect N1 and P2 amplitudes and latencies. We suggest most studies show abnormalities of vertex potentials in schizophrenia, but certainly some do not. Thus, the results in this study of abnormalities in the N1 and P2 elicited by standards in an oddball task do not mean that N1 and P2 in all tasks will be similarly reduced. It remains important to examine the N1 and P2 elicited by single tones with and without attention to determine the degree to which “sensory” components of N1 and P2 are affected early in the disease. For example, based on the topography of P2b described by O’Donnell et al,2 we infer P2b abnormalities may be present in first-hospitalized patients. We cannot, however address purely sensory aspects of P2 using the current task and analysis. Our previous work showed no reduction of MMN in a subset of these patients at first hospitalization (Salisbury et al 2004) and that MMN reduction developed during the early course of the disease37. By contrast, P3 was reduced at first hospitalization38. The vertex potentials here were reduced at first hospitalization. Although N1 and P2 are typically referred to as sensory potentials, they occur much later than the initial afferent signals to the auditory cortex and were measured from an attention-dependent task. It may be that the ERPs (N1, P2, MMN, P3) are sensitive to different underlying pathologies in different generator sites with different time courses. On the other hand, it may be that the MMN, generally thought to be preattentive, may not be as affected at first hospitalization as attention-related potentials like the N1 and P2 here and P3. First hospitalization likely postdates the actual onset of symptoms and may in fact miss the actual first psychotic episode. Although determination of prodrome onset would be optimal, we did not have reliable methods or the infrastructure necessary for such a determination during the time this data were collected. The standard method in the literature for reliable determination of onset is when symptoms are severe enough to require hospitalization, which has the advantage of being extremely objective.

In summary, N1 and P2b are reduced in FHSz patients, similarly to chronically ill patients, on an auditory oddball target detection ERP task with relatively slow presentation rates (1.2-s ISI). These classic vertex potentials may thus serve as potential endophenotype that are easy to record. The presence of deficits in first-hospitalized patients is necessary but not sufficient for establishing N1 and P2 as endophenotypes and is only one of the necessary criteria. Further research examining these potentials in family members (crucial for demonstrating genetic links) and using single-tone AEP tasks (crucial for isolating “sensory” generators) is warranted. With regard to the underlying neurophysiology, research is currently underway to examine whether the reductions in N1 and P2b amplitude can be associated with differences in phase synchrony. This is of some importance, as determining whether this difference reflects structural cortical generator loss or functional local cortical circuit derangement has implications for understanding the pathophysiology of schizophrenia.

Funding

Department of Veterans Affairs (Merit Award, Schizophrenia Center Award, R.W.M.); National Institute of Health (R01 MH 40799, R01 MH 052807, R01 MH 058704 to R.W.M.; R01 MH 858704 to D.F.S.); Mental Illness and Neuroscience Discovery foundation (to R.W.M.); and The National Alliance for Research in Schizophrenia and Depression (to D.F.S.).

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