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First-Episode Schizophrenic Psychosis Differs From First-Episode Affective Psychosis and Controls in P300 Amplitude Over Left Temporal Lobe

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Abstract

Background—Schizophrenia is associated with central (sagittal) midline reductions of the P300 cognitive event-related potential and topographic asymmetry of P300, with reduced left temporal voltage. This P300 asymmetry is, in turn, linked to tissue volume asymmetry in the posterior superior temporal gyrus. However, it is unknown whether P300 asymmetry is specific to schizophrenia and whether central and lateral P300 abnormalities are due to chronic morbidity, neuroleptic medication, and/or hospitalization, or whether they are present at the onset of illness.

Methods—P300 was recorded in first-episode schizophrenia, first-episode affective psychosis, and control subjects (n=14 per group). Subjects silently counted rare (15%) target tones (1.5 kHz) among trains of standard tones (1.0 kHz). Averages were constructed from brain responses to target tones.

Results—Peak amplitude of P300 and integrated voltage over 300 to 400 milliseconds were significantly different between first-episode schizophrenics and controls over the posterior sagittal midline of the head. First-episode schizophrenics displayed smaller amplitudes over the left temporal lobe than first-episode affective psychotics and controls, but the groups showed no differences over the right temporal lobe.

Conclusions—Left-sided P300 abnormality in first-episode schizophrenia relative to first-episode affective psychosis and controls suggests that P300 asymmetry is specific to schizophrenic psychosis and present at initial hospitalization. This P300 asymmetry suggests left temporal lobe dysfunction at the onset of schizophrenia.
Numerous studies using midline electrode sites and an “oddball task” (detecting rarely presented target stimuli from among standards) have shown that decrement in auditory-elicited P300 amplitude in schizophrenia is robust.\textsuperscript{4,5}

The scalp-recorded P300 has multiple brain generators. At least 3 sets of bilateral generators must be proposed to explain P300 topography. Squires et al\textsuperscript{6} demonstrated 2 distinct waves constituting P300: an earlier, frontally distributed potential (P3a); and a later-onset, posteriorly maximal wave (P3b). Recent work indicates at least 2 posterior sources for P3b. Several lines of evidence are consistent with a source in the temporal lobe. Although early studies\textsuperscript{7–10} focused on sub-cortical areas, recent work suggests the primary sources are cortical in nature. Knight et al\textsuperscript{11} found that stroke lesions that include the superior temporal gyrus (STG) abolish auditory P300. In addition, P300 topography did not change after medial temporal lobectomy.\textsuperscript{12,13} Moreover, direct cortical recordings\textsuperscript{14} revealed dissociations between limbic- and scalp-recorded P300. As well, cortical recordings in humans suggest that the major temporal lobe source of posterior P300 lies in STG, with another source in inferior parietal lobule.\textsuperscript{9,10,15–17} Due to its location in the left posterior STG, an area related to language processing, comprehension, and thought, this particular P300 generator may be especially useful for detecting abnormal left temporal lobe function in schizophrenia.

### PATIENTS AND METHODS

#### PATIENT RECRUITMENT

Patients were referred from the McLean First-Episode Psychosis Project\textsuperscript{44} or recruited from the inpatient population of McLean Hospital, Belmont, Mass. The medical records of consecutive admissions to the hospital were examined weekly. A total of 347 patients entering the hospital with psychotic features for the first time or transferred within 3 months of first hospitalization for psychosis were selected for further screening. Of those patients, 145 met criteria for age (18–55 years); IQ (above 75); normal hearing (assessed by audiometry); right-handedness; and no history of seizures, head trauma with loss of consciousness, neurological disorder, and alcohol or drug dependence. Of those patients meeting criteria, 45 consented to participate. Diagnoses were made utilizing the Structured Clinical Interview for \textit{DSM-III-R} (SCID)\textsuperscript{45} and by review of hospital course. One patient was dropped due to technical failure during ERP recording, 2 patients were judged never psychotic, and 3 patients presented in a schizoaffective state. Of the remaining 39 patients, 14 received Axis I diagnoses for schizophrenia (10 men and 4 women); the remainder, either bipolar disorder or depression with psychotic features. An age-matched group of 14 first-episode affective disordered patients (12 men and 2 women; 10 bipolar, manic; 2 bipolar, mixed; and 2 major depressive disorder, all with psychotic features) and an age-matched group of 14 psychiatrically normal controls (SCID Non-Patient Edition,\textsuperscript{46} SCID-II Personality Disorders\textsuperscript{47}; 12 men and 2 women) were compared with the first schizophrenic episode group. Initial SCIDs were administered to half of the patients by an independent group (headed by M.T.) blinded to ERP measures. Diagnoses on the remainder were made prior to ERP recording (M.E.S. and D.F.S.), and videotaped for a third opinion (R.W.M.) when necessary. Due to the uncertainty inherent in diagnosis at first hospitalization, patients were reinterviewed between 6 and 12 months following initial testing. Twelve patients received a full SCID in the laboratory. Eleven patients received an abbreviated telephone interview. Two patients were rehospitalized and diagnoses confirmed then. Three patients were lost to follow-up; 1 left the country, 1 committed suicide, and 1 refused to return. For these 3 patients, initial diagnoses were used. At the second interview, all 25 remaining patients continued to meet diagnostic criteria for either schizophrenia or affective psychosis, including illness duration and persistent decline in social functioning. Table 1 presents a SCID-based symptom checklist and indicates all items met for all patients. Note that...
whereas all patients exhibited psychosis, groups showed quite different affective symptomatology.

All subjects gave informed consent and were paid to participate. All patients were tested during hospitalization for an acute psychotic episode. All testing was conducted in 1 session. All subjects performed the Mini-Mental State Examination to rule out any dementia or delirium, the information subscale of the Wechsler Adult Intelligence Scale–Revised as a gross estimate of fund of information, and the digits forward and backward subscales of the Wechsler Adult Intelligence Scale–Revised to test immediate/short-term memory, attention, and concentration. Subject characteristics and test scores are presented in Table 2. First-episode schizophrenics showed significantly lower socioeconomic status than controls, consistent with lowered social and occupational capacity. The parental socioeconomic status of schizophrenics was significantly lower than the parental socioeconomic status of affective psychotics. Groups performed nearly identically on the Mini-Mental State Examination. Compared with controls, schizophrenics displayed a smaller fund of information, and affective psychotics showed poorer digits backward performance.

ERP TESTING

Subjects silently counted binaurally presented target tones (97 dB, 1.5 kHz, 50-millisecond duration, 10-millisecond rise and fall times, 15% of trials) among standard tones (97 dB, 1.0 kHz) against a background of 70-dB white noise. Tones were presented with an interstimulus interval of 1.2 seconds. Electroencephalographic activity was recorded from the scalp through 28 tin electrodes in preconfigured caps (Electro-Cap International Inc, Eaton, Ohio). Linked-earlobes were used as the reference, the forehead as ground. Two electrodes located medially to the right eye, 1 above and 1 below, were used to monitor vertical eye movements. Electrodes placed at the outer canthi of the eyes were used to monitor horizontal eye movements. All electrode impedances were below 3 kΩ, and the ears were matched within 1 kΩ. The electroencephalograph 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 3.516 milliseconds per sample. Each epoch lasted 900 milliseconds, including a 100-millisecond prestimulus baseline. Averaging and artifact rejection were performed offline. Epochs were digitally low-pass filtered at 8.5 Hz with 24 dB per octave roll-off to remove ambient electrical noise, muscle artifact, and alpha contamination. Within each 200-trial block, epochs were baseline corrected by subtraction of the average prestimulus voltage. Vertical and horizontal eye movement artifacts were corrected with regression-based weighting coefficients only if the standard deviation of the correction factor was 0.009 µV or less. Subsequently, epochs that contained voltages exceeding ±50 µV at F7, F8, Fp1, or Fp2 were rejected. Averages were computed from the brain responses to target tones. P300 was measured in 2 ways: peak P300 amplitude, which accounts for individual variations in P300 latency, was measured as the most positive point from 250 to 650 milliseconds at each recording site; and integrated P300 amplitude during a static 100-millisecond window (300–400 milliseconds after stimulus) for comparability with our previous analyses in chronic schizophrenia.

ANALYSES

One-way analysis of variance (ANOVA) with post hoc Scheffé tests were conducted to assess group differences in demographic, clinical, basic neuropsychological, and task performance measures. For P300, mixed-model repeated-measures ANOVA was used to test for effects along the sagittal midline of the head and over the temporal lobes. Subsequent one-way ANOVA with post hoc Scheffé tests were conducted in cases of significant group effects and group by side interactions. Results were considered significant at $P \leq 0.05$, corrected where factors had more than 2 levels with the Huynh-Feldt $\varepsilon$. 

Arch Gen Psychiatry. Author manuscript; available in PMC 2009 August 24.
Despite a wealth of evidence for midline P300 amplitude reduction in schizophrenia,\textsuperscript{5,18,19} there are few studies examining P300 early in the disease. Midline P300 reductions have been reported in young and unmedicated schizophrenics.\textsuperscript{20–23} In the only report of ERPs in first-episode psychosis, visual sensory potentials were not abnormal.\textsuperscript{24} P300 responses elicited at first psychiatric admission have never been reported.

In addition to midline P300 reductions, chronically ill schizophrenics display asymmetry in P300, with smaller voltage over the left (T3) vs the right (T4) temporal lobe.\textsuperscript{25–27} The P300 asymmetry originally reported by Morstyn et al\textsuperscript{25} has been replicated by several other researchers.\textsuperscript{28–33} This effect is present when patients are medicated\textsuperscript{26–33} and unmedicated.\textsuperscript{34} Other groups have failed to replicate left temporal scalp area P300 reduction in schizophrenia.\textsuperscript{35,36} Bruder et al\textsuperscript{28} suggested that task demands may play a role, based on the demonstration by Polich\textsuperscript{37} of largest P300 when subjects silently counted target stimuli, stating that all studies using silent counting reported P300 asymmetry but that only 2 of 5 studies using a button press found it. However, a recent study using silent count did not report a left temporal P300 deficit in schizophrenics,\textsuperscript{38} but the experimental protocol differed in that patients were supine with eyes closed. In addition, McCarley et al\textsuperscript{39} showed that there was normal P300 topography in those schizophrenics with the largest STG volumes. Thus, response mode and patient selection may play a role in failure to replicate. In summary, most studies examining P300 topography in schizophrenia found left temporal reduction, but several studies did not, likely due to differences in methods. In studies that found P300 asymmetry, left temporal P300 amplitude (from the midtemporal T3 site) correlated negatively with the extent of psychiatric symptoms (Thought Disorder Index scores\textsuperscript{40} and delusions\textsuperscript{41}). Gray matter volume in the combined left amygdala and hippocampus, and left posterior STG was reduced in schizophrenics, but only left STG volumes were correlated positively with P300 amplitude.\textsuperscript{39} Left STG volume was, in addition, correlated negatively with Thought Disorder Index scores\textsuperscript{42} and severity of auditory hallucinations.\textsuperscript{43} Therefore, abnormal left temporal P300 may reflect underlying STG abnormality and index the severity of psychotic symptoms and serve as a physiological tie between underlying brain pathology and psychosis.

It is not known whether P300 abnormalities are present at disease onset. P300 abnormalities may be due to any or all sequelae of illness: chronic morbidity, long-term neuroleptic treatment, long-term hospitalization, among others. As well, it is not known whether left temporal reductions in P300 voltage are specific to schizophrenia or appear in other psychotic disorders, such as those associated with affective disorder. The presence of lateral P300 reductions at first schizophrenic episode, but not at first episode of affective psychosis, would imply underlying abnormalities of the left temporal lobe specific to schizophrenia at disease onset. To determine whether topographic abnormalities and midline reductions of P300 voltage were present at the initial onset of and specific to schizophrenia, ERPs were recorded from patients entering the hospital for treatment of psychotic symptoms for the first time (first-episode schizophrenia or affective psychosis) and from psychiatrically normal control subjects.

**RESULTS**

For target count, all groups were 90\% accurate, but the schizophrenic group’s performance (93.2\% accurate) was significantly worse than that of affective psychotics (98.5\%) and controls (99.3\%) (\(P < .01\)). Including accuracy as a covariate had no effect on the significance levels reported below. The mean number of trials used to construct target averages did not differ significantly between groups, with approximately 20 trials surviving artifact rejection.

Grand averaged ERPs to target tones are presented in Figure 1. Groups were significantly different in peak P300 along the sagittal midline (Fz, Cz, and Pz; \(F_{2, 30} = 4.8, P < .01\)). Post hoc tests revealed that P300 amplitude in schizophrenics was significantly smaller than that of
controls at Cz and Pz. Patients with affective disorders were not significantly different from either of the other groups, nor were there any significant group differences at Fz. All 3 groups showed the expected posterior distribution of P300 (F_{2,78}=84.5, P,.001, \varepsilon=0.90, no group by site interaction). Of primary importance are group differences at lateral temporal sites. Analysis of peak P300 amplitude at the left and right temporal sites revealed significant group differences (F_{2,39}=5.8, P=.006). There was a significant interaction between group and side of the head (F_{2,39}=4.64, P=.016). Post hoc tests revealed that P300 amplitude at the left temporal site (T3) in the schizophrenic group was significantly smaller than in the other groups. Groups were not significantly different at the right temporal site (T4). Peak amplitudes and latencies are presented in Table 3, along with integrated voltages (see below).

To obviate any confounding between overall group peak amplitude differences and lateral topographical differences, lateral analyses were conducted on normalized peak data. Each lateral voltage was normalized by dividing by the mean group Cz amplitude (thus, all voltages are expressed relative to Cz, which has a mean of 1 for each group). There were no overall significant group differences and no main effect of side. There was a significant interaction between group and side (F_{2,39}=5.30, P=.009). Expressed relative to Cz amplitude, the schizophrenic group was smaller on the left side than the right (0.43 vs 0.58), in contrast to the affective group (0.66 vs 0.49) and the controls (0.48 vs 0.39).

Integrated P300 amplitude from 300 to 400 milli-seconds from all scalp electrodes were used to construct the topographic maps presented in Figure 2, A. Maps are normalized for each group so that zero voltage is blue and maximum voltage is magenta. The topography of P300 in first-episode schizophrenics was abnormally asymmetrical compared with both other groups, showing a deficit in P300 voltage on the left side. Analysis of integrated amplitude along the midline (Fz, Cz, and Pz) revealed significant group differences (F_{2,39}=5.2, P=.01). Post hoc tests revealed significant differences between schizophrenics and controls at Cz and Pz. All groups showed the expected posterior distribution of P300 (F_{2,78}=75.3, P,.001, \varepsilon=0.92, no group by site interaction). Analysis of lateral sites revealed significant differences between groups (F_{2,39}= 3.8, P=.031) and a significant group by side interaction (F_{2,39}=3.4, P=.043). Post hoc tests revealed that the schizophrenic group was significantly smaller than the other groups at T3, but no groups were significantly different at T4. Figure 2, B, shows the absolute differences between groups in integrated P300 amplitude. The schizophrenic group showed the largest absolute amplitude differences from both control and affective psychosis groups at posterior midline and left temporal areas. Control and affective psychosis groups showed maximum differences over frontocentral midline areas. Figure 2, C, presents the significance levels associated with the absolute group differences. The first-episode schizophrenic group showed greatest statistically significant separation from the other groups at left temporal sites. Control and first-episode affective psychosis groups showed no statistically significant differences anywhere on the head.

Group distributions of peak and integrated P300 amplitude at temporal electrode sites are presented in Figure 3. Groups showed separation in both peak and integrated P300 voltages over the left temporal site (T3), with first-episode schizophrenia distributions shifted to-ward smaller values. Over the right temporal site (T4) distributions showed greater overlap. Differences in P300 amplitude cannot be ascribed to outliers in the schizophrenic group.

**COMMENT**

Posterior midline P300 reductions were present in first-episode schizophrenics. Statistically significant midline reductions were not present in first-episode affective psychotics (mostly mania with psychotic features), although values were intermediate with schizophrenics and controls. Schizophrenics also showed abnormal P300 topography at disease onset, with voltage
decrement over left temporal lobe. First-episode affective psychotics showed no abnormal asymmetry, with left temporal amplitudes larger than right (compare with Bruder et al\textsuperscript{28} and Souza et al\textsuperscript{31}).

P300 asymmetry in first-episode schizophrenia cannot be explained by secondary effects of psychosis on cognitive function. Both patient samples were psychotic, but asymmetry was present only in schizophrenics. If the P300 reductions were due to general cognitive dysfunction, then widespread P300 reduction over the whole surface of the head would be expected. The unilateral reduction of P300 over the left temporal lobe suggests a regionally selective effect that is not secondary to general cognitive deficits. This reduction does, we think, index disturbed cognitive functions related to the left temporal lobe. Salisbury et al\textsuperscript{27} showed that P300 amplitude at T3 remained reduced in patients with chronic schizophrenia despite changes in performance and reaction time with changes in stimulus discriminability, demonstrating dissociation of left temporal P300 amplitude from other functional measures. This is likely due to dysfunction of left-sided generators, particularly STG, in that our previous work\textsuperscript{39} showed a correlation between volume reduction of this cortical area and lateral P300 reduction in patients with chronic schizophrenia.

Posterior midline voltage reduction in schizophrenia, which reflects abnormalities of summed activity from each bilateral set of generators, may be due to unilateral abnormalities, namely, the failure of left-sided generators to contribute to central summed activity. The pattern of relative P300 amplitudes from the normalized data set supports this because the schizophrenic group had the largest mean relative value of T4 amplitude and the smallest mean relative value at T3. This suggests that there are unequal contributions from lateral sources to Cz amplitude, because if both lateral sources were reduced, then the relative proportion of voltage at both sides should be small, or at least roughly equal.

We hypothesize that P300 is reduced over left temporal scalp areas in schizophrenia due to a smaller amount of cortical gray matter in the left posterior STG. The abnormality is not due to lowered concentration, lack of attention, task difficulty, or general cognitive and widespread brain dysfunction, but to a localized structural abnormality in schizophrenia.\textsuperscript{39} This is not meant to imply that every schizophrenic has a left P300 deficit or that this deficit exists singularly. Schizophrenia likely involves abnormalities in a distributed network including the frontal and temporal lobes.\textsuperscript{55} Structural abnormalities in the temporal lobe could cause a distributed functional abnormality, such that other cortical operations in the network show irregularities due to abnormal feed-forward information. As well, it is likely that other structural abnormalities exist, particularly in the frontal lobe.\textsuperscript{56–58}

Unequivocal relation of scalp-recorded P300 to underlying generator abnormalities cannot be made. Since underlying brain was not directly measured, the inference that first-episode schizophrenics, who as a group show left temporal P300 reduction, also show underlying cortical gray matter volume reduction of left posterior STG remains tentative. Currently, we are examining a new sample of first-episode patients with ERP and magnetic resonance imaging measures to replicate the P300 asymmetry reported in this study and to extend the research by directly examining the relationship between scalp-recorded P300 and cortical gray matter. Another limitation relates to the generalizability of left temporal P300 amplitude reduction in schizophrenia to female patients. We included women in this sample, although too few to make meaningful comparisons of gender. In a mostly female schizophrenic group (12 women and 6 men), Bolsche et al\textsuperscript{59} recently reported that all schizophrenics showed a shift in P300 maxima to the right, but specific comparison of T3 and T4 were not performed. Also, Weisbrod et al\textsuperscript{32} showed left P300 reduction at T3 in a mostly female schizophrenic group (8 women and 3 men). Since few studies have included women, additional studies are needed to examine left temporal area scalp P300 reduction in schizophrenic women.
The presence of left-sided P300 abnormality in first-episode schizophrenia, but not in first-episode affective psychosis, suggests that topographic abnormalities over the left temporal lobe are specific to schizophrenia and are present at the initial manifestation of psychopathology. This left temporal P300 asymmetry in first-episode schizophrenia implies underlying left temporal lobe dysfunction at disease onset and involvement of left temporal lobe dysfunction in the etiology of schizophrenia. The P300 voltage asymmetry may reflect asymmetrical posterior STG, with smaller volumes in the left temporal lobe. However, this inference is tentative, and future magnetic resonance imaging studies are needed. From the pattern of P300 scalp topography observed in this study, we conclude that left temporal lobe P300 reduction is present in a group of first-episode schizophrenic patients, but is not present in a group of first-episode affective psychotic patients. Thus, left temporal area scalp P300 reduction is not associated with psychosis in general, is selectively present in schizophrenic groups, and, therefore, may be an objective physiological measure of schizophrenic psychopathology present at disease onset.

Acknowledgments

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Figure 1.
Target event-related potential waveforms from each group. P300 is reduced over the left temporal lobe (T3) in first-episode schizophrenics relative to first-episode affective psychotics and controls, but not over the right temporal lobe (T4).
Figure 2.
A, Integrated P300 scalp topography from 300 to 400 milliseconds. The first-episode schizophrenic group shows an asymmetrical distribution with unilateral left temporal reductions. B, Absolute group differences. The first-episode schizophrenic group shows the greatest differences from the other groups over the left temporal areas. C, When variance of grand averages is taken into account, the greatest statistically significant group differences are localized to lateral left temporal sites. Pointers on scale bars indicate color above which differences exceed \( P=0.05 \) ( \( t \) test, \( df=26 \)); NS, not significant.
Figure 3.
Scattergrams of P300 amplitudes (integrated from 300 to 400 milliseconds [A] and peak [B]) for each group at temporal electrode sites. P300 amplitude distributions at left temporal sites are shifted to lower values in first-episode schizophrenics.
Table 1

<table>
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<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14</td>
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*SCID indicates Structured Clinical Interview for DSM-III-R; checkmark, 3 on the SCID; and BC, broadcasting.
Table 2

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<th>Control(n=14)</th>
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<tr>
<td>Parental SES</td>
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<td>1.1±0.3</td>
<td>1.3±0.9</td>
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<td>Mini-Mental §</td>
<td>28.9±1.1</td>
<td>29.1±1.2</td>
<td>28.9±0.9</td>
<td>.77</td>
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<tr>
<td>WAIS-R information¶</td>
<td>19.3±5.1</td>
<td>22.5±4.6</td>
<td>24.6±3.7</td>
<td>.01</td>
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<tr>
<td>WAIS-R digits forward</td>
<td>8.9±2.6</td>
<td>8.2±1.6</td>
<td>9.0±1.9</td>
<td>.54</td>
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<td>WAIS-R digits backward</td>
<td>6.5±2.9</td>
<td>5.6±1.3</td>
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<td>Global Assessment Scale§</td>
<td>36.9±12.5</td>
<td>35.7±13.4</td>
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<tr>
<td>Brief Psychiatric Rating Scale§</td>
<td>36.0±4.7</td>
<td>36.4±8.1</td>
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<tr>
<td>Medication (CPZ equiv)</td>
<td>239.6±223.0</td>
<td>138.6±72.5</td>
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<td>.12</td>
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</tbody>
</table>

* ANOVA indicates analysis of variance; CPZ equiv, chlorpromazine equivalent.
† Edinburgh Inventory 48: −1 indicates left-handed; 1, right-handed.
‡ Socioeconomic status 49: 5 indicates lowest; 1, highest; post hoc Scheffé tests indicate only schizophrenic and control groups’ SES differ at P< .05, and parental SES of schizophrenics and affective psychotics differ at P< .05.
§ Groups significantly differ at P< .05 using post hoc Scheffé tests.
¶ Summed scores on the Mini-Mental State Examination 50: score range, 0 to 30.
§§ Summed raw scores on the Wechsler Adult Intelligence Scale-Revised 51: results of post hoc Scheffé tests indicate that only schizophrenic and control groups’ information subscale scores were different at P< .05, and affective psychotics and controls were significantly different on digits backward subscale at P< .05.
<table>
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<tr>
<th></th>
<th>Fz</th>
<th>Cz</th>
<th>Pz</th>
<th>T3</th>
<th>T4</th>
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<tr>
<td><strong>Peak 300 amplitude, µV</strong></td>
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<td>3.5*f</td>
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<td>14.0</td>
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<td><strong>Integrated voltage, µV</strong>†</td>
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<td>413.0</td>
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<td>405.5</td>
</tr>
</tbody>
</table>

* Schizophrenic and control groups differ significantly, P < .05.
† Schizophrenic and affective psychotic groups differ significantly, P < .05.
‡ Integrated voltage from 300 to 400 milliseconds.