ORIGINAL ARTICLE

Left Temporal Lobe Dysfunction in Schizophrenia

Event-Related Potential and Behavioral Evidence From Phonetic and Tonal Dichotic Listening Tasks

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Background: Asymmetric reduction of the P3 event-related potential (ERP) has provided evidence of left temporal lobe dysfunction in schizophrenia. Prior studies have been limited by reliance on simple target detection (oddball) tasks with pure tones. This study investigated the time course and topography of ERPs to binaural syllables or complex tones in dichotic listening tasks.

Methods: Event-related potentials of 26 patients meeting criteria for schizophrenia (n = 19) or schizoaffective disorder (n = 7) and 26 healthy controls were recorded from 30 scalp electrodes during 2 dichotic tasks in which different syllables or complex tones were simultaneously presented to each ear. A principal components analysis was used to derive factor scores corresponding to overlapping components in ERP waveforms—N1, N2, P3, and a late-positive potential.

Results: Healthy controls showed a right ear advantage for perceiving dichotic syllables, which was associated with greater N2 amplitude at left than right temporoparietal sites. Patients with schizophrenia did not show either this perceptual or N2 asymmetry. Patients also had smaller late-positive potential amplitude when compared with controls for both syllables and complex tones, with greatest decrement over left temporal sites.

Conclusions: A right ear advantage in healthy adults for perceiving consonant-vowels was associated with a left-lateralized ERP component peaking at 200 milliseconds after syllable onset (N2). Patients with schizophrenia failed to show either of these task-dependent asymmetries, which may indicate a dysfunction of left temporal regions involved in phonetic classification. A task-independent asymmetric reduction of a later positive potential in patients with schizophrenia resembled left temporal P3 reductions reported for auditory oddball tasks.

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EVENT-RELATED potentials (ERPs) measure brain electrical activity that is time-locked to the onset of stimuli in cognitive tasks and can therefore provide unique information about neurophysiologic processes underlying cognitive dysfunctions in schizophrenia.[1] The task used in most studies is a simple target detection (oddball) task, in which an infrequent target tone is intermixed with frequent nontarget tones. Event-related potential components that occur at different latencies after onset of the target tones reflect the sequence of information processing, beginning with early sensory processing, as reflected by a negative N1 component peaking at about 100 milliseconds. Initial stimulus classification is indexed by a negative N2 component peaking at about 200 milliseconds. Later stages of cognitive processing (eg, stimulus evaluation) are reflected in the late-positive (LP) complex, which consists of overlapping subcomponents, including the well-known P3 component. Amplitudes of these ERP components generally have been found to be reduced in patients with schizophrenia when compared with healthy controls.[2-10]

Event-related potential reductions in schizophrenia are intriguing because of the involvement of medial and lateral temporal lobe regions in the generation or modulation of auditory ERPs,[11-16] combined with evidence of hippocampal and superior temporal gyrus abnormalities in schizophrenia.[5,17-22] Reductions of N2 and P3 amplitudes in schizophrenia have been related to reduced volume of superior temporal gyrus or more medial structures (eg, hippocampus) in magnetic resonance images.[2,6,23,24] Some studies indicate that P3 reductions in schizophrenia are larger over left than over right temporal lobe sites,[5,25,26] while other studies have found equal P3 reductions over each hemisphere.[3,8]

SUBJECTS AND METHODS

SUBJECTS

Twenty-six right-handed patients from the Schizophrenia Research Unit of the New York State Psychiatric Institute, New York, and 26 normal controls were tested. The patients met criteria of the *DSM-IV*[35] for schizophrenia (undifferentiated, n = 11; paranoid, n = 5; disorganized, n = 3); schizoaffective disorder (bipolar type, n = 4); or schizoaffective disorder (depressive type, n = 3). Data for the patients with schizophrenia and schizoaffective disorder were pooled for the analyses reported in this article. When analyses of the ERP data were repeated after excluding patients with schizoaffective disorder, all patient vs control differences for N1, N2, and late positivity reported below for the full sample remained statistically significant. The patient group included 16 men and 10 women who ranged in age from 20 to 55 years, with a mean (SD) age of 33.2 (10.9) years, and had a mean (SD) education level of 13.3 (3.1) years. Research diagnoses were made on the basis of information provided from clinical interviews and from a semistructured interview by a trained and reliable rater using the Diagnostic Interview for Genetic Studies.[36] This interview schedule includes the items from other commonly used instruments (eg, Structured Clinical Interview for *DSM-III-R*, Patient Edition,[37] The Scale for the Assessment of Positive Symptoms,[38] and The Scale for the Assessment of Negative Symptoms[39]). A consensus diagnosis was made by the rater and a senior clinician (X.A.). At the time of testing, 18 of the patients were receiving antipsychotic medications: 4 patients were receiving haloperidol (mean dosage, 13.1 mg/d; range, 7.5-20 mg/d), 3 patients were receiving thiothixene (mean dosage, 18.3 mg/d; range, 15-20 mg/d), 2 patients were receiving fluphenazine hydrochloride (mean dosage, 25.0 mg/d; range, 20-30 mg/d), 2 patients were receiving perphenazine (mean dosage, 46 mg/d; range, 32-60 mg/d), 1 patient was receiving trifluoperazine hydrochloride (40 mg/d), 3 patients were receiving risperidone (mean dosage, 5.3 mg/d; range, 3-9 mg/d), 2 patients were receiving clozapine (mean dosage, 512.5 mg/d; range, 450-575 mg/d), and 1 patient was receiving olanzapine (20 mg/d). The remaining 8 patients (4 with schizophrenia and 4 with schizoaffective disorder) did not receive antipsychotic medications for an average of 4 weeks (mean, 28.1 days; range, 13-61 days) prior to testing.

Control participants were screened using a modified version of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version[40] to exclude those with current or past psychopathologic disorders. This group consisted of 13 men and 13 women who ranged in age from 20 to 60 years (mean [SD] 35.5 [11.7] years) and had a mean (SD) education level of 15.6 (1.8) years. There was no significant difference in mean age between the patient and control groups, $F_{1,48} < 1.0$, but the patient group had significantly less education than the controls, $F_{1,48} = 10.18$, $P < .005$. However, education was not significantly associated with either performance or ERP measures in this study. All controls and patients were right-handed, as indicated by their laterality scores on the Edinburgh inventory.[41] They received an audiometric evaluation to exclude those with a hearing loss (>30 dB at 500, 1000, or 2000 Hz) or a difference between ears of more than 10 dB. They were also screened to exclude those with a history of neurological insult or illness, a substance abuse problem, or a history of substance abuse that obscured diagnosis. Written informed consent was obtained from each participant.

DICHOTIC LISTENING TASKS

Event-related potentials were recorded during 2 analogous dichotic listening tasks, 1 using consonant-vowel syllables and the other using complex tones. In each task, a different syllable or tone was presented simultaneously to the 2 ears, followed by a binaurally presented probe syllable or tone. The probe was either the same as 1 member of the dichotic pair or different from both. The subject's task was to press a response button if the probe matched 1 of the dichotic syllables or tones. The beginning of each trial was indicated by the appearance of a cross in the center of a television monitor. Subjects were instructed to fixate their eyes on the cross. One second after the cross appeared, the dichotic pair of syllables or tones were presented, and 2 seconds later the probe syllable or tone was presented. The subject was required to respond during a 3-second interval that was indicated by the disappearance of the cross from the television monitor 1.5 seconds after the probe stimulus. Trials in each task were arranged in 6 blocks, with 32 trials per block in the syllable task and 28 trials per block in the tone task. In each block, half of the probe stimuli matched a member of the dichotic pair, and there were equal numbers of left ear and right ear matches. Two practice blocks (binaural and dichotic) preceded the test blocks.

For the tonal task, there were 8 different complex tones with a duration of 250 milliseconds and a rise/decay time of 25 milliseconds. Tones consisted of square waves with fundamental frequencies corresponding to the major notes in the octave between middle C (264 Hz) and C5 (528 Hz). The tones were digitally synthesized using a commercial software package (STIM; Neuroscan Inc, Herndon, Va)[42] to match the stimuli in the complex tone test.[43] For the syllable task, 6 consonant-vowel syllables (*/da/*, */ba/*, */ta/*, */pa/*, */ka/*, */ga/*) spoken in a male voice were digitized from a recording of a standard dichotic syllable test (for a description of the physical properties of these stimuli, see Berlin et al[44]). While the syllables were already matched for duration and intensity for use in the dichotic listening test, they were further edited to match the duration and root mean squared amplitude of the tonal stimuli. All stimuli were presented binaurally at 72-dB sound pressure level via a matched pair of earphones (TDH-49 earphones; Northeastern Technologies, Glen Cove, NY) that were calibrated for

A limitation of ERP studies of schizophrenia has been the reliance on simple oddball tasks with pure tones. The use of more challenging tasks, in particular tasks that require the differential involvement of left or right hemisphere regions, may provide new insights into the role of lateralized temporal lobe dysfunction in schizophrenia. Dichotic listening tests, in which a different stimulus is simultaneously presented to the 2 ears, typically yield a right ear (left hemisphere) advantage for perceiving syllables or words and a left ear (right hemisphere)

loudness. Earphone orientation, response hand, and task order were counterbalanced across subjects.

ERP RECORDING

Electroencephalograms were recorded from 4 midline (Fz, Cz, Pz, Oz) and 26 homologous electrode placements from both hemispheres (Fp1 and Fp2, F3 and F4, F7 and F8, FT9 and FT10, FC5 and FC6, C3 and C4, T7 and T8, TP9 and TP10, CP5 and CP6, P3 and P4, P7 and P8, P9 and P10, O1 and O2) by using a nose reference with a Fpz ground and impedances maintained at 5 κΩ or less (for electrode nomenclature of the 10-20 system, see Pivik et al[45]). Electroencephalogram gain was 10 000, with a .01- to 30-Hz band pass (–6 dB/octave). Data were sampled for 1280 milliseconds at 100 Hz (prestimulus baseline, 200 milliseconds), and low-pass filtered offline at 20 Hz (–24 dB/ octave). Electrooculograms were recorded differentially from the outer canthi of each eye (horizontal bipolar) and from supraorbital and infraorbital sites (vertical bipolar).

DATA REDUCTION AND ANALYSIS

This article presents the ERPs recorded to binaural probe stimuli that were correctly identified as the same as a member of the dichotic pair or as different. Trials contaminated by artifacts were eliminated when electroencephalogram or horizontal electrooculogram data exceeded ±100 µV after blink correction.[46] Average ERP waveforms were computed for each participant and each task (syllable and tone tasks) and each stimulus condition (same and different) for valid trials with correct responses. The mean (SD) numbers of trials for syllable and tone tasks, respectively, after artifact rejection were 98.8 (25.4) and 90.4 (25.3) for patients, and 123.0 (21.7) and 108.0 (32.5) for controls. Despite the greater loss of trials for patients, the number of patient trials after artifact rejection was sufficient to yield ERP waveforms of quality comparable to that for normal controls.

Averaged ERP waveforms were submitted to a principal components analysis (PCA) derived from the covariance matrix, followed by a varimax rotation, to determine the sources of variance in the ERP waveforms.[32,47,48] This method ideally results in the generation of distinctive, triangle-shaped, weighted time windows (ie, the factor loadings), which more efficiently describe variance contributions of temporally and spatially overlapping ERP components than do conventional ERP component measures (eg, the mean amplitude in a latency window).[32,47] The factor analysis was computed using BMDP statistical software.[49] Columns of the data matrix represented time (110 sample points from –100 to 1000 milliseconds), and rows represented the participants (52), tasks (2), conditions (2), and electrode sites (30). The number of orthogonal factors extracted by the PCA was limited by a criterion of eigenvalues greater than 1.0, allowing extraction of 23 factors, explaining 99.8% of the ERP variance, including low variance noise factors. The first 4 principal components accounted for 90.6% of the variance (**Figure 1**). Peak latencies of PCA factor loadings and topographies of PCA factor scores largely corresponded to ERP components present in the average waveforms (**Figure 2** and **Figure 3**) and will be described in the order of their peak latencies. Factor 4 (2.2% explained variance) peaked at 100 milliseconds and almost entirely overlapped the N1 peak in the ERP waveforms. Analogously, factor 3 (5.9% explained variance) peaked at approximately 200 milliseconds and corresponded to the N2 peak. The next 2 factors accounted for much of the variance in the LP complex. Factor 2 (39.0% explained variance), with a peak latency of about 500 milliseconds, corresponded closest to the P3 peak in the ERP waveforms. Factor 1 (43.4% explained variance) extended over a relatively long period and reached its maximum amplitude at about 800 milliseconds after stimulus onset. It closely corresponded to a LP slow potential seen in the ERP waveforms and will be referred to as the LP potential. Additional PCAs were performed separately on the patient and control group data, and on the data for each task. The resulting principal components were essentially the same as the original 4 PCA factors in peak latency and topography, thereby confirming that the factors adequately represented the variance of ERPs for each group in both tasks.

Principal components analysis factor scores were submitted to repeated measures analysis of variance (ANOVA) with group (patient/control) and response hand (left/right) as between-subjects factors, and task (syllable/tone), condition (same /different), hemisphere (left/right), and site (13 symmetric pairs of electrodes, excluding midline electrodes) as within-subjects factors. Greenhouse-Geisser ϵ correction was used to evaluate F ratios for within-subject effects involving more than 2 *df*.[50] Significant interactions involving site were examined through simple effects at each site to locate the source of the interaction.[49] Significant group differences in component topography were confirmed in separate ANOVA after vector scaling the amplitudes for each task (ie, across hemisphere and site).[51]

Topographic maps were generated with commercial software (NeuroScan, Version 3.0; NeuroScan Inc, Herndon, Va)[52] by linear interpolation of mean factor score amplitudes for each of the 30 recording sites from the 4 nearest electrodes. Maps were plotted for the sole purpose of illustrating group differences in ERP topographies indicated by significant interactions in the repeated measures ANOVA.

For analyses of the behavioral data, the percentage of correct responses (ie, when the subject responded to a match between the probe stimulus and a member of the dichotic pair) was computed for right and left ear matches to dichotic syllables or tones. Analogous to analyses of ERP data, performance percentages were submitted to a repeated-measures ANOVA with group (patient/control) and response hand (left/right) as between-subjects factors, and task (syllable/tone) and ear (left/right) as within-subjects factors, followed by analyses of simple effects.

Pearson correlations were computed to examine the relationship of prominent ERP findings and behavioral performance. Significant correlations were validated with nonparametric Spearman rank-order correlations.

In all analyses, a conventional α level of $P<.05$ was applied.

advantage for complex pitch perception in healthy adults.[27] Studies have generally found less right ear advantage for dichotic words or syllables in patients with schizophrenia when compared with either patients with depression or healthy adults.[28-30] Although these findings are consistent with the hypothesis that schizophrenia involves dysfunction of left temporal lobe areas specialized for processing language-related stimuli,[19] more direct measures of regional hemispheric activity are needed to evaluate this hypothesis.

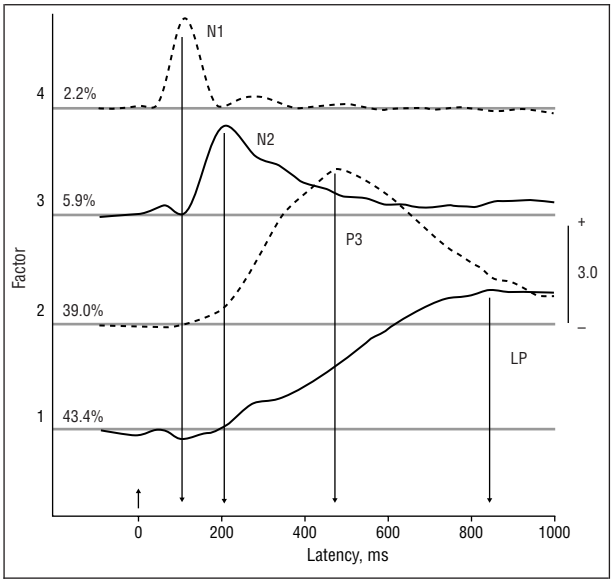

Figure 1. *Varimax rotated factor loadings plotted over time for 4 orthogonal factors extracted by principal components analysis: N1, N2, P3, and late positivity (LP). Factors were ordered according to their peak latencies rather than to the percentage of explained variance, which largely depends on time period and electrode locations covered by a factor. Factor labels were chosen to reflect both the time course of the factor loadings and the polarity of the associated event-related potential components.*

A preliminary study[31] measuring ERPs during a dichotic complex tone task supported findings of a left-lateralized P3 reduction in schizophrenia.[5] However, the recording montage was inadequate to detail the topography of the effect, and no syllable or word task was used. Recent studies in healthy adults have demonstrated regional hemispheric asymmetries of N2 and P3 consistent with the known neuroanatomical organization of phonetic and tonal processing.[32-34] The purpose of this study was to record ERPs of patients with schizophrenia and normal controls during both dichotic syllable and complex tone tests. The use of 30 electrode placements enabled us to examine the scalp distribution of ERPs during the phonetic and tonal tasks, and to define differences in ERP topography between patients with schizophrenia and healthy controls.

RESULTS

BEHAVIORAL DATA

Overall, performance was better for tones when compared with syllables (main effect task, $F_{1,48} = 60.19$, $P < .001$), and there was also a trend for a group by task interaction ($F_{1,48} = 3.63$, $P = .06$). Analyses of simple effects for each task revealed that normal controls showed the expected right ear (left hemisphere) advantage for perceiving dichotic syllables (simple main effect ear, $F_{1,48} = 6.23$, $P = .02$), whereas patients showed no difference in accuracy across ears (see **Figure 4**). Patients had significantly poorer accuracy for perceiving syllables when compared with controls (simple main effect group, $F_{1,48} = 5.91$, $P = .02$). Although there was only a nonsignificant trend for a group by ear interaction for syllables ($F_{1,48} = 2.93$, $P = .09$), the group difference in accuracy was significant for right ear syllables ($F_{1,48} = 8.22$, $P = .006$), but not for left ear syllables ($F_{1,48} = 1.91$, $P = .17$). There was no significant difference between groups in accuracy for perceiving dichotic tones in either the right or left ear (simple main effects group, each $F_{1,48} < 1.0$).

AVERAGE ERP WAVEFORMS AND COMPONENT STRUCTURE

Grand average ERP waveforms for patients and normal controls in the tonal and syllable tasks are shown in Figures 2 and 3. These figures show the amplitude and latency of ERP components that occurred following stimulus onset at each of the 30 electrode sites. The N1 component, a negative peak with a latency of about 100 milliseconds, was most prominent at the midline frontal (Fz) and central (Cz) sites in each task. A smaller N2 component, with a peak latency of about 200 milliseconds, was maximal in amplitude at lateral temporoparietal sites (eg, TP9, P7) in the syllable task. N2 was followed by a broadly distributed LP complex with maximum amplitude over parietal sites (eg, Pz). This consists of a P3 peak about 500 milliseconds after stimulus onset followed by an LP slow potential.

N1 COMPONENT

As shown in Figures 2 and 3, patients had considerably smaller N1 amplitude than controls. This group difference was confirmed by a repeated measures ANOVA performed on factor scores corresponding to the N1 component ($F_{1,48} = 26.01$, $P < .001$). The N1 reduction was maximal at frontocentral sites where N1 is largest (group by site interaction, $F_{12,576} = 11.48$, $P < .001$, $\epsilon = .21$) and was equally present at electrode sites over each hemisphere. At frontocentral sites, the N1 reduction in patients was larger in the tone task than in the syllable task (group × site × task, $F_{12,576} = 4.16$, $P = .01$, $\epsilon = .20$).

N2 COMPONENT

Patients also showed a smaller N2 amplitude when compared with controls ($F_{1,48} = 7.05$, $P = .01$), which was most evident for the syllable task at electrode sites over the left hemisphere (group × task × hemisphere interaction, $F_{1,48} = 5.97$, $P = .02$). Analyses of simple effects revealed that this 3-way interaction was due to the presence of a task × hemisphere interaction for controls ($F_{1,48} = 6.52$, $P = .01$), but not for patients ($F_{1,48} < 1.0$). Normal controls showed greater N2 amplitude over the left than right hemisphere sites in the syllable task (simple main effect hemisphere, $F_{1,48} = 6.25$, $P = .02$), but not in the tone task, whereas patients did not show this task-dependent N2 asymmetry. These differences in N2 amplitude and asymmetry between patients and controls were also dependent on electrode site, being most evident over temporoparietal sites (group × task × hemisphere × site interaction, $F_{12,576} = 2.62$, $P = .03$, $\epsilon = .35$).

The difference in N2 between groups for the syllable task and the dependence on electrode site and hemisphere are shown in **Figure 5**, which includes topographic maps of factor scores corresponding to N2. The

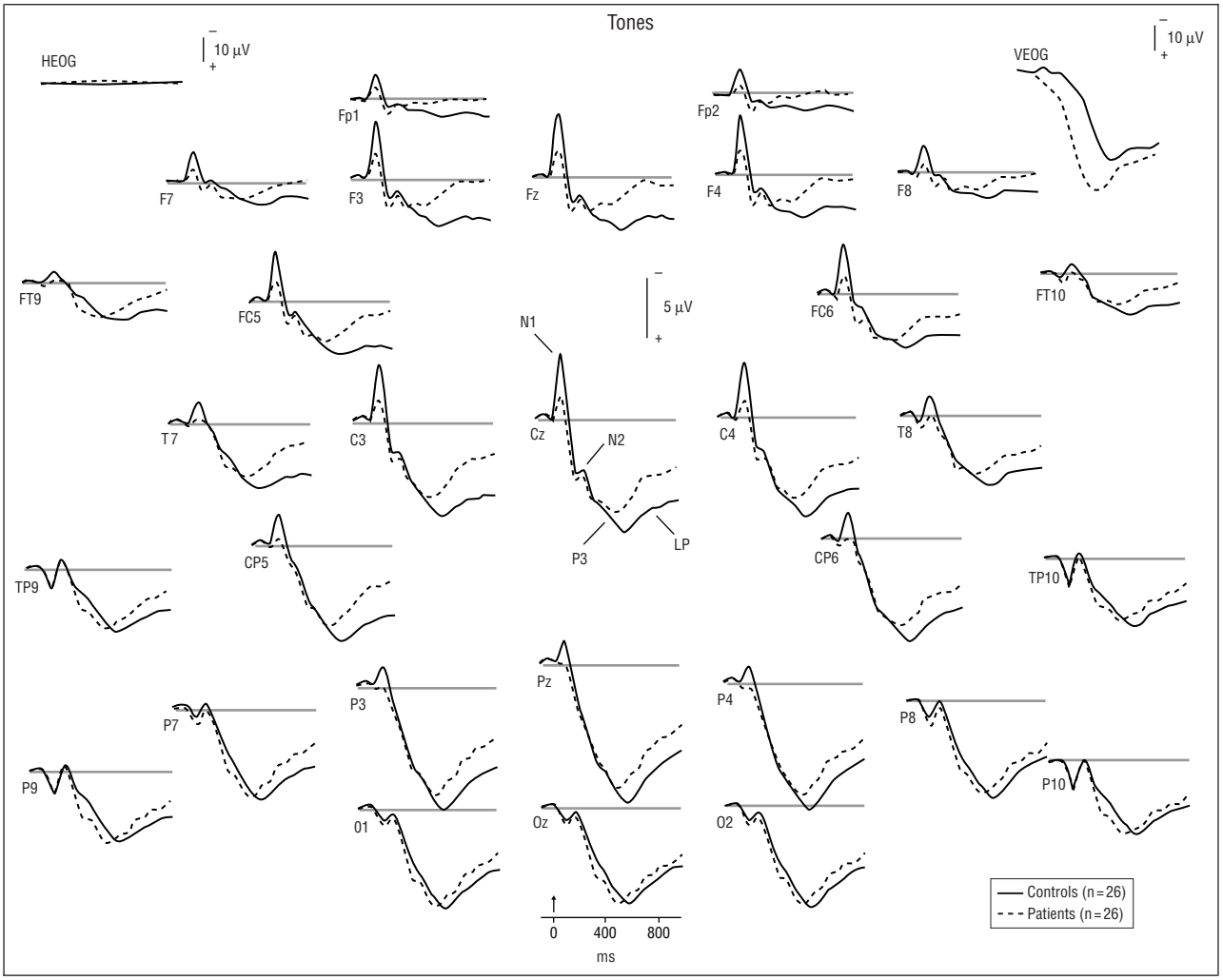

Figure 2. *Grand average event-related potential waveforms from 30 electrode sites for 26 patients and 26 controls to probe tones in the complex tone task. Recording sites covered the whole scalp, including anterior-frontal (Fp1, Fp2), lateral-temporal (T7, T8), lateral-parietal (P7, P8), and occipital areas (O1, Oz, O2). Electrode nomenclature follows the International 10-20 System,[45] where odd numbers refer to left and even numbers to right hemisphere sites. Event-related potential components are indicated at Cz (central site). Note the different scaling for horizontal (H) and vertical (V) electro-oculogram (EOG) channels showing EOG averages before artifact removal.*

dark blue regions in the topographic map for normal controls show left temporoparietal sites where N2 was greatest in the syllable task. This N2 asymmetry was less evident in the topographic map for patients. Moreover, the difference in N2 amplitude between controls and patients (Figure 5, right) was clearly greatest over the left temporoparietal sites, ie, the dark blue region.

The N2 asymmetry at temporoparietal sites was related to the perceptual asymmetry for dichotic syllables. The average N2 asymmetry at temporoparietal sites, where there were significant task-dependent differences in N2 asymmetry between groups (ie, T7/8, TPg/10, CP5/6, P7/8, Pg/10), was significantly correlated with the behavioral laterality quotient ($LQ = 100 \times [R–L]/[R+L]$, where R and L are the percentage of correct matches for right and left ears) in the syllable task. Across all subjects, greater N2 amplitude over left than right temporoparietal sites was associated with having a right ear (left hemisphere) advantage for perceiving dichotic syllables ($r = –0.42$, $P = .002$). This relationship held equally for patients ($r = –0.41$, $P = .04$) and controls ($r = –0.45$, $P = .02$). As shown in **Figure 6**, the same percentage (73%) of normal controls had a right ear (left hemisphere) advantage for perceiving syllables as had a greater N2 amplitude over left than right temporoparietal sites. In contrast, the perceptual and N2 asymmetry scores for patients cluster around 0, which is consistent with a lack of a left hemisphere advantage for processing consonant-vowel syllables. Asymmetry scores for 8 patients who were tested while not taking antipsychotic medication (open circles in Figure 6) suggest that the lack of a left hemisphere advantage in patients was not due to the medications.

P3 COMPONENT

One subcomponent in the LP complex peaked at about 500 milliseconds and was of maximum amplitude at parietal sites (see Figures 2 and 3). It has the same scalp distribution as the classic P3b component seen in oddball tasks.[1,53] Its longer latency in the dichotic listening task than in the oddball task (ie, 500 vs 300 milliseconds) is likely due to task differences (eg, difficulty of

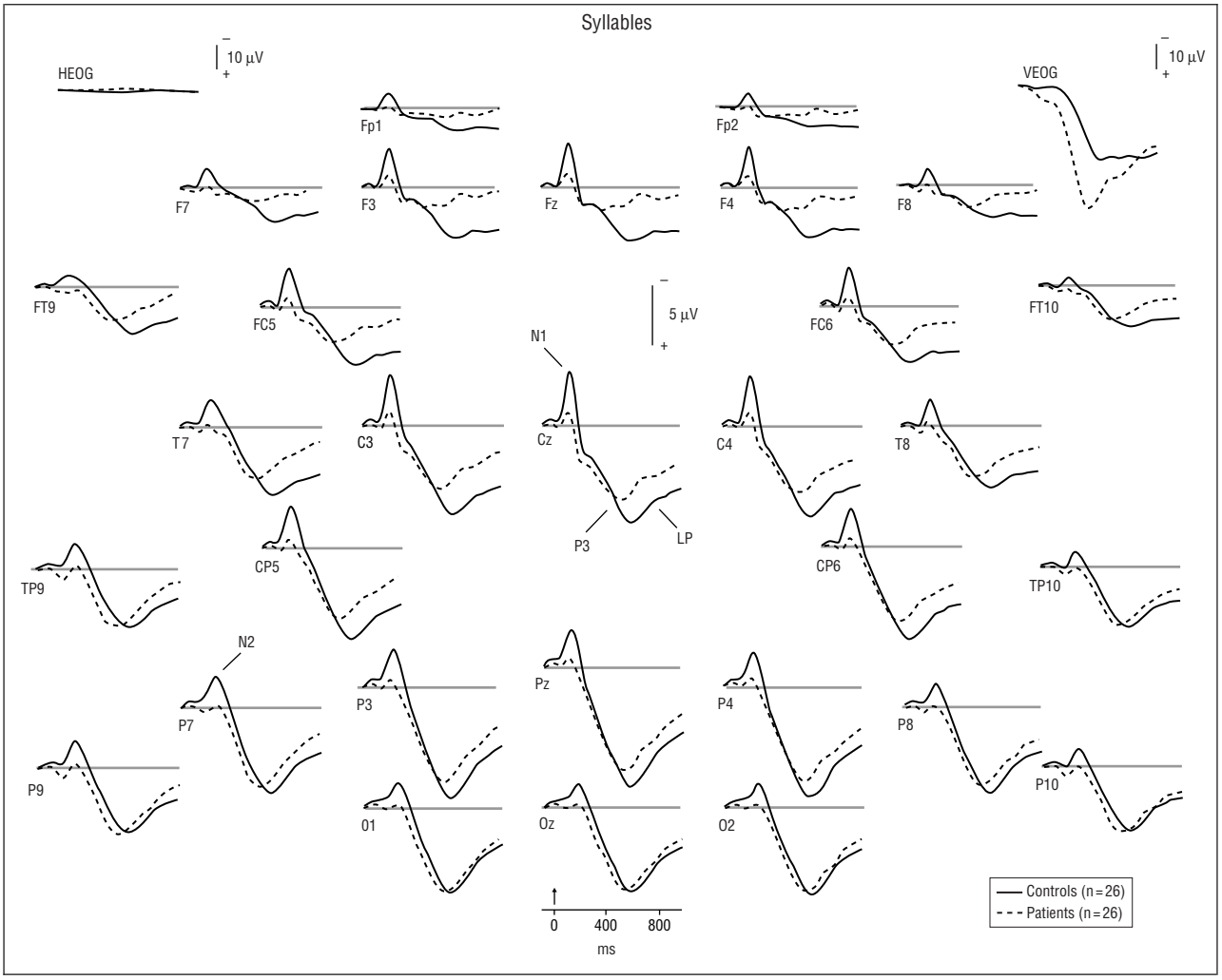

Figure 3. *Grand average event-related potential waveforms from 30 electrode sites for 26 patients and 26 controls to probe syllables in the consonant-vowel task. Event-related potential components are indicated at Cz and P7. See the legend to Figure 2 for explanation of abbreviations.*

stimulus discrimination or delayed response). An ANOVA of the factor scores corresponding to the P3 component did not reveal any group difference in the amplitude of this component. There was a significant site effect ($F_{12,576} = 55.85$, $P < .001$, $\epsilon = .18$) reflecting the parietal maximum of P3, a condition effect ($F_{1,48} = 10.23$, $P = .002$) reflecting the greater P3 amplitude for probe stimuli that were correctly judged to be the "same" as a member of the dichotic pair, and a condition × site interaction ($F_{12,576} = 25.86$, $P < .001$, $\epsilon = .21$) reflecting the posterior distribution of this effect. The only significant interaction involving group was group × condition × hemisphere ($F_{1,48} = 9.57$, $P = .003$). Analysis of simple effects showed that there was a significant group × hemisphere interaction for correct "same" judgments ($F_{1,48} = 5.95$, $P = .02$), but not for "different" judgments ($F_{1,8} < 1.0$). Normal controls showed greater P3 amplitude over the right than left hemisphere for same judgments ($F_{1,48} = 6.35$, $P = .01$), whereas patients did not ($F_{1,48} < 1.0$). Neither group showed a significant hemispheric asymmetry of P3 for different judgments (both $F_{1,48} < 1.0$).

LP COMPONENT

The LP component consisted of a slow wave potential that overlapped the P3 component and extended to the end of the recording epoch (see Figure 1). Unlike the P3 component, it had a central-parietal scalp distribution (main effect site, $F_{12,576} = 27.06$, $P < .001$, $\epsilon = .20$) and a greater positive amplitude to probe stimuli that were correctly judged to be different from each stimulus of the dichotic pair ($F_{1,48} = 5.67$, $P = .02$). As can be seen in Figures 2 and 3, patients had markedly smaller LP amplitude when compared with controls (main effect group, $F_{1,48} = 8.60$, $P = .005$). Moreover, the reduction of LP amplitude in patients was greater over left than right hemisphere sites (group × hemisphere interaction, $F_{1,48} = 5.79$, $P = .02$). The scalp topography of the LP component for each group and the difference in its amplitude between groups is shown in **Figure 7**. The red region in the map for normal controls shows the central and parietal sites where they had the largest LP amplitudes, and the map for patients shows less LP amplitude than controls. The red region in the group difference map (right portion of

Figure 7) identifies the left temporal sites where patients had the greatest LP reductions.

COMMENT

Patients with schizophrenia failed to show a right ear advantage for perceiving dichotic consonant-vowel syllables, which confirms prior reports of reduced or absent left hemisphere superiority for perceiving syllables or words in schizophrenia.[28-30,54] Most importantly, the millisecond resolution of ERPs allowed us to specify the timing of neurophysiologic activity associated with this abnormal perceptual asymmetry. The amplitude of the N2 component, occurring about 200 milliseconds after syllable onset, was greater over left than right inferior temporoparietal sites in healthy adults, but not in patients with schizophrenia. The inference that this N2 asymmetry is associated with left hemisphere superiority for language-related processing was supported by significant correlations between N2 asymmetry and right ear advantage for perceiving dichotic syllables. Recently, Näätänen et al[55] have found language-specific mismatch negativities in the left auditory cortex by using magnetoencephalography recordings during phoneme perception. Moreover, these functional asymmetries are not modality-specific; another magnetoencephalography study[56] reported a localized activation of left inferior temporal-occipital regions about 180 milliseconds after visual presentation of a word in healthy adults, and intracranial recordings from the inferior temporal lobe have revealed word-specific responses about 200 milliseconds after word onset.[57] In a visual word recognition memory task, we have found greater N2 amplitude at left than right inferior parietal sites in healthy adults, but not in patients with schizophrenia.[58] The presence of a left-lateralized N2 in normal controls for consonant-vowel syllables, but not complex tones, is consistent with the view that it represents an electrophysiologic correlate of the initial phonetic categorization of the syllables.[32,59] The lack of perceptual or N2 asymmetry in patients with schizophrenia may reflect a deficit in left-lateralized phonological processing of speech stimuli, similar to that reported for subjects with dyslexia.[56]

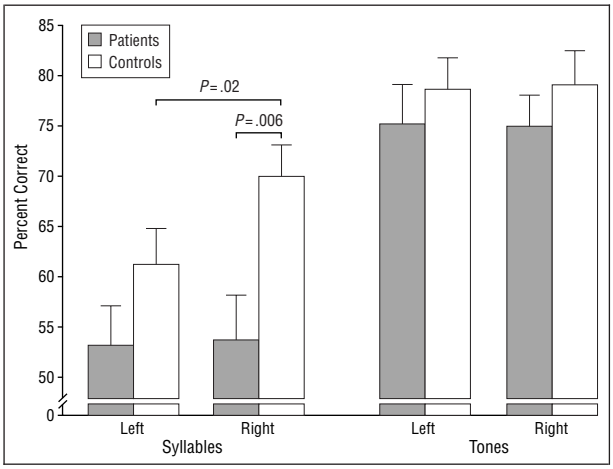

Figure 4. *Percentage of correct responses for 26 patients and 26 controls for probe stimuli matching left or right items in the dichotic syllable or tone pairs. Significant simple effects within each task are indicated by brackets.*

Patients with schizophrenia also showed abnormalities of the LP complex. A PCA extracted 2 overlapping subcomponents: (1) a positive peak resembling the classic P3b component, which had maximum amplitude at parietal sites and a latency of about 500 milliseconds; and (2) an LP slow potential, which had a widespread centroparietal distribution, extending laterally into temporal sites, and a broader time course, reaching its maximum during the later half of the recording epoch. In accordance with our preliminary findings for the complex tone task,[31] the reduction of late positivity in schizophrenia was largest over left hemisphere sites. The PCA revealed that this left-lateralized reduction was not due to the parietal-maximum P3 subcomponent, but rather to the overlapping LP slow potential. Turetsky et al[26] used a different approach to identify frontal, temporal, and parietal subcomponents of P3. A left-lateralized reduction was found for the temporal lobe subcomponent, but not for the frontal or parietal subcomponents. The possibility that the left-lateralized reduction in late positivity may

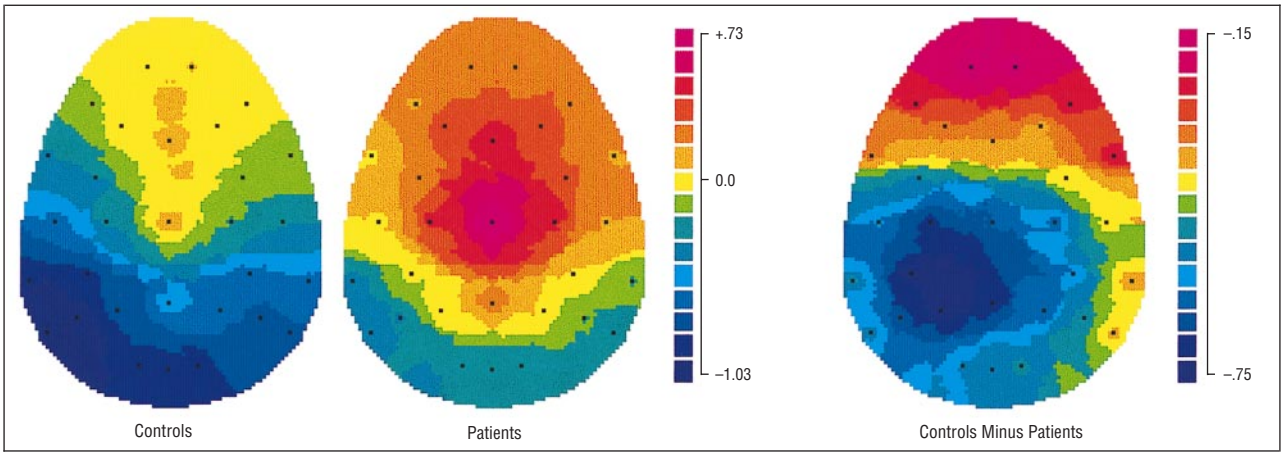

Figure 5. *Left, Topographies of principal components analysis (PCA) factor scores corresponding to N2 for 26 controls and 26 patients to probe syllables in the consonant-vowel task (left hemisphere sites are on the left side of each map). The sign of the factor scores reflects the polarity of the underlying event-related potential component. Negative scores (blue through green regions) are associated with greater N2 amplitude. Right, Corresponding group difference map (controls minus patients). Black dots on each map correspond to electrode sites defined in the legend of Figure 2.*

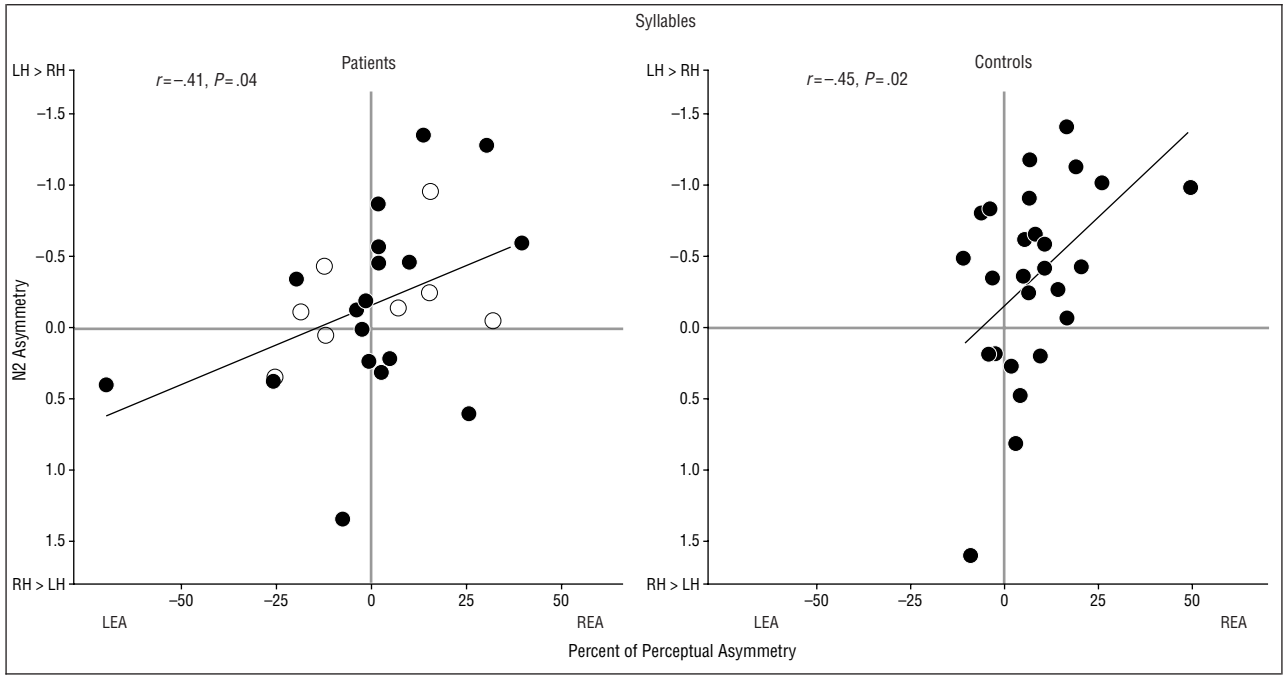

Figure 6. *Scattergrams showing the relationship between hemispheric asymmetry of N2 at temporoparietal sites and perceptual asymmetry for 26 patients and 26 controls for the syllable task. Hemispheric differences in N2 amplitude (left minus right) indicate the extent of left hemisphere (LH) or right hemisphere (RH) advantage. Left ear advantage (LEA) and right ear advantage (REA) refer to the direction of perceptual asymmetry scores (100 [R–L]/[R+L]). Open circles indicate patients not receiving medication.*

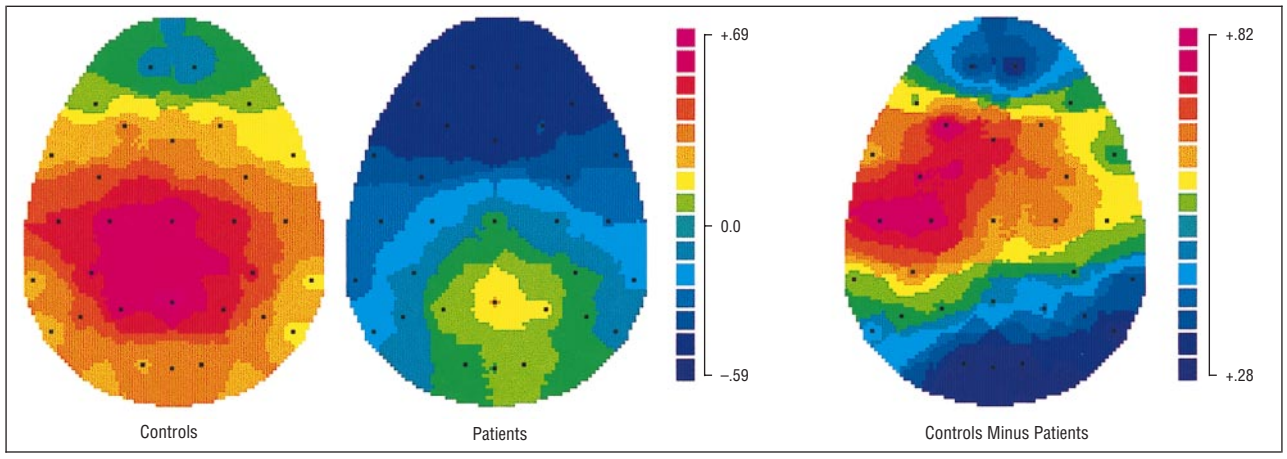

Figure 7. *A, Topographies of principal components analysis (PCA) factor scores corresponding to the late-positive (LP) potential for 26 controls and 26 patients averaged across the syllable and tone tasks (left hemisphere sites are on the left side of the maps). Positive scores (red through yellow regions) are associated with greater LP amplitude. B, Corresponding group difference map (controls minus patients). Black dots on each map correspond to electrode sites defined in the legend of Figure 2.*

be specific to schizophrenia is suggested by absence of this abnormality in patients who have either a bipolar disorder with mania[31] or a depressive disorder[60] who were tested on the dichotic complex tone test. Recently, Salisbury et al[25] reported that first-episode patients with schizophrenia showed an abnormal P3 topography remarkably similar to the topography of LP reduction seen in this study, but first-episode patients having an affective psychosis did not show this left-lateralized deficit.

The findings illustrate how ERPs can provide useful information about the time course and topography of neurocognitive dysfunctions in schizophrenia. This study does, however, have limitations that will need to be addressed in future research. First, the sample of patients with schizophrenia in this study was not large enough to deal with the issue of clinical heterogeneity. Dichotic listening studies suggest that reduced left hemisphere advantage for perceiving words or syllables is more evident in patients who have hallucinations than in patients who do not,[28,30] and differences in dichotic laterality have been found between diagnostic subtypes, ie, patients with paranoid vs nonparanoid schizophrenia[61] and between subgroups formed on the basis of variability in heart rate.[62] Second, the dichotic complex tone test failed to yield the expected left ear (right hemisphere) advantage previously observed in healthy adults.[34,43,63] This limits the conclusions that can be drawn concerning hemispheric dominance for complex pitch perception in schizophrenia. Three studies using nonverbal dichotic tasks agreed in finding the normal left ear (right hemi-

sphere) advantage in patients with schizophrenia,[64-66] and studies using visuospatial tasks have found the normal left visual field (right hemisphere) advantage in schizophrenic patients.[54,67] Third, although the reduction of N2 amplitude in schizophrenic patients was largest during the syllable task at left temporoparietal sites covering cortical regions traditionally associated with language perception,[68] caution must be exercised in making inferences about the specific structures that underlie this left-lateralized ERP deficit. Whether the absence of the N2 or perceptual asymmetry for syllables is related to a deficit of specific temporal lobe structures (eg, an abnormal asymmetry of the planum temporale)[19,69] remains to be determined. Studies using ERP or magnetoencephalography measures in conjunction with neuroimaging (eg, magnetic resonance imaging or positron emission tomographic scans) can provide both the temporal and spatial resolution needed to better address this objective.

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