
Event-Related Brain Potentials (ERPs) in Schizophrenia for Tonal and Phonetic Oddball Tasks

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Background: *Prior studies using simple target detection (“oddball”) tasks with pure tones have reported asymmetric reduction of the P3 event-related potential (ERP). This study investigated the time course and topography of ERPs recorded during both tonal and phonetic oddball tasks.*

Methods: *Event-related potentials of 66 patients (14 unmedicated) diagnosed with schizophrenia (n = 46) or schizoaffective disorder (n = 20) and 32 healthy adults were recorded from 30 scalp electrodes during two oddball tasks using consonant–vowel syllables or complex tones. Overlapping ERP components were identified and measured by covariance-based principal components analysis.*

Results: *Schizophrenic patients showed marked, task-independent reductions of early negative potentials (N1, N2) but not reduced P3 amplitude or abnormal P3 asymmetry. Task-related hemispheric asymmetries of the N2/P3 complex were similar in healthy adults and schizophrenic patients. Poorer task performance in patients was related to ERP amplitudes, but could not account for reductions of early negativities.*

Conclusions: *The findings suggest that both patients and control subjects activated lateralized cortical networks required for pitch (right frontotemporal) and phoneme (left parietotemporal) discrimination. Task-independent reductions of negativities between 80 and 280 msec after stimulus onset suggest a deficit of automatic stimulus classification in schizophrenia, which may be partly compensated by later effortful processing.* Biol Psychiatry 2001;49:832–847 © 2001 Society of Biological Psychiatry

Key Words: Schizophrenia, event-related potentials (ERPs), N2/P3 complex, hemispheric asymmetries, tonal/phonetic oddball tasks, principal components analysis (PCA)

Introduction

One of the most consistent findings of event-related potential (ERP) research in schizophrenia has been a reduction of the late positive P3(00) component in simple auditory target detection (“oddball”) tasks (e.g., for a recent review, see Ford 1999). Earlier negative ERP components (e.g., N1, N2) and components of target minus nontarget difference waveforms (e.g., mismatch negativity, N2d) are also reduced in schizophrenic patients (e.g., Catts et al 1995; Ford et al 1994; Javitt et al 1995; O’Donnell et al 1993; Potts et al 1998; Roth et al 1980, 1991; Salisbury et al 1994; Shagass et al 1977; Shelley et al 1991, 1999). Event-related potentials create an important link between cognitive and neural processes because they provide a functional measure of electrical brain activity that occurs time locked to a significant event, with ERP components reflecting successive stages of information processing (e.g., Pfefferbaum et al 1995). P3 amplitude, for instance, is generally thought to index a late cognitive process (e.g., stimulus evaluation) and, accordingly, to be an electrophysiologic correlate of cognitive dysfunction in schizophrenia. Several clinical features have been associated with reduced P3 amplitude in schizophrenia, including both trait and state aspects of illness severity (e.g., Mathalon et al 2000a; Strik et al 1993b; Turetsky et al 1998a), illness duration and age of onset (Mathalon et al 2000b), negative symptoms (e.g., Pfefferbaum et al 1989; Strik et al 1993b), and thought disorder (e.g., Ford et al 1999; Iwanami et al 2000). However, the specific origins for ERP alterations in schizophrenia, whether psychological/behavioral, neurostructural/neurochemical, or both, are still uncertain. It is also unclear to what extent reduced P3 amplitude—or other ERP abnormalities—mark a deficit specific to schizophrenia, as similar reductions have also been associated with other disorders featuring cognitive impairments, among them major depression, alcoholism, or dementia, and also with normal aging (e.g., Picton 1992).

Neuroanatomical and neurophysiological evidence strongly suggest that multiple intracranial sources contribute to the generation or modulation of auditory ERPs.

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Subcomponents of the N2/P3 complex are linked to neuronal activity of frontal and temporoparietal brain regions, including the superior temporal gyrus (with auditory cortex) and posterior superior parietal gyrus, and the hippocampus (Halgren et al 1998; Knight 1990; Menon et al 1997). With magnetic resonance imaging (MRI), abnormalities of the above temporal lobe structures have often been reported for schizophrenia (for a review, see McCarley et al 1999). Moreover, asymmetric N2 and P3 reductions in schizophrenia, with smaller amplitudes over left temporal sites relative to right ones, were accompanied by asymmetric abnormalities in temporal lobe structures (e.g., McCarley et al 1991, 1993; O'Donnell et al 1993, 1999; Salisbury et al 1998; Turetsky et al 1998b). Other studies in schizophrenia have reported symmetric P3 reductions over each hemisphere (e.g., Ford et al 1994; Pfefferbaum et al 1989), and MRI data for some of these patients also showed comparable volume reductions of both temporal lobes (e.g., Zipursky et al 1994; see also Ford 1999).

Not all studies, however, have found significant P3 reductions in schizophrenia during simple auditory oddball tasks (e.g., Kathmann et al 1995; Mathalon et al 2000b; Strik et al 1993a) or have reported even greater P3 amplitudes in patients (Strik et al 1997). When task requirements were individually adjusted for a subject's discrimination ability, schizophrenic patients showed P3 amplitude equal to control subjects in the "target-button press" (go) condition (Weisbrod et al 2000). Directly addressing the controversy of asymmetric (i.e., left-lateralized) versus symmetric P3 amplitude reduction in schizophrenia, Hill and Weisbrod (1999) reported a correlation between hemispheric asymmetry and overall amplitude in schizophrenic patients: left-sided reductions were associated with low overall P3 amplitude and accounted for amplitude differences among patients. The same relation between P3 amplitude and asymmetry was apparent in the data for 20 schizophrenic patients after they were grouped according to syndromal features (Gruzelier et al 1999).

Most auditory ERP studies in schizophrenia have relied on a classic oddball paradigm with binaural pure tones, implicitly assuming that such a cognitive task requires equal hemispheric processing resources or that any lateralized processing effects are similar across groups, and that paradigm requirements (e.g., response mode) play a subordinate role for investigating the basic phenomenon (i.e., reduced P3). However, recent studies in right-handed healthy adults have found regional hemispheric asymmetries of N2 and P3 consistent with the known neuroanatomic organization of phonetic and tonal processing (Alexander et al 1996; Bruder et al 1999; Tenke et al 1993), and these task-related ERP asymmetries were modulated by response requirements (i.e., left- or right-hand press)

(Kayser et al 1998; Tenke et al 1998). This dissociation of N2 and P3 topographies during simple oddball tasks using tonal or phonetic stimuli creates an ideal opportunity to more directly study lateralized neurophysiologic processes underlying cognitive dysfunctions in schizophrenia. The purpose of this study was therefore to compare ERP findings for healthy adults during tonal and phonetic oddball tasks with those for a large sample of schizophrenic patients. Functional ERP abnormalities in schizophrenia were investigated with respect to time course, by using temporal principal components analysis (tPCA) to disentangle the sequence of overlapping ERP components that are thought to correspond to discrete stages of information processing, and with respect to scalp topography, by using a 30-channel recording montage. If ERP abnormalities in schizophrenia reflect a language-related, left-sided deficit involving the supratemporal plane (e.g., Crow 1997), we would expect such abnormalities to be particularly evident in a phoneme discrimination task on which healthy adults show distinct N2 and P3 topographies indicative of left parietotemporal activation (Kayser et al 1998). In contrast, a pitch discrimination task, for which healthy adults show N2 and P3 asymmetries indicative of right frontotemporal activation, should show less ERP abnormalities in schizophrenia. The comparably large patient sample also enabled us to examine these hypotheses with respect to diagnostic subtypes and clinical symptoms, which are to be reported elsewhere (Bruder et al, submitted).

Behavioral performance in schizophrenic patients is generally poorer than in healthy adults. However, most ERP studies have paid little attention to how this poorer (and less consistent) performance in cognitive tasks may impact on ERP measures. Group differences in behavioral performance in these tonal and phonetic oddball tasks were therefore explicitly examined as a potential moderator of ERP differences.

Methods and Materials

Participants

Table 1 summarizes the sample's major demographic and clinical characteristics. Only right-handed participants were included in the study, as indicated by the laterality scores on the Edinburgh Inventory (Oldfield 1971). Participants were excluded if they had a hearing loss (>30 dB at 500, 1000, or 2000 Hz) or difference between ears (>10 dB), a history of neurologic insult or illness, or current or past episodes of substance abuse. Written informed consent was obtained from each participant. Participants yielding fewer than 15 valid trials in any experimental condition after ERP data processing were excluded.

SCHIZOPHRENIC PATIENTS. Sixty-six inpatients (43 male, 23 female) from the Schizophrenia Research Unit of New

Table 1. Means, SDs, and Ranges for Demographic and Clinical Variables

Variable	Schizophrenic patients (<i>n</i> = 66, 43 male)			Healthy adults (<i>n</i> = 32, 18 male)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	33.8	10.5	19–60	35.3	11.9	20–60
Education (years)	13.0 ^a	3.0	7–24	15.5	2.0	11–21
Handedness (LQ)	83.0	22.0	10–100	83.9	14.6	57–100
Onset age (years)	21.3 ^b	6.3	12–39			
Illness duration (years)	12.7 ^c	9.6	0–47			
Total BPRS	34.3 ^d	8.3	19–54			
PANSS general	28.1 ^d	6.4	16–43			
PANSS positive	15.3 ^d	5.9	7–30			
PANSS negative	15.7 ^d	6.0	7–31			

LQ, laterality quotient (range –100 to 100; Oldfield 1971); BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.

^aPatients differ significantly from healthy adults ($p = .0002$).

^b*n* = 59.

^c*n* = 58.

^d*n* = 60.

York State Psychiatric Institute were recruited for this study. Event-related potential data collected in different paradigms had been previously reported for approximately half of these patients (Bruder et al 1998, 1999; Kayser et al 1999). The patients met DSM-IV (American Psychiatric Association 1994) criteria for schizophrenia (undifferentiated, *n* = 27; paranoid, *n* = 13; disorganized, *n* = 6) or schizoaffective disorder (bipolar type, *n* = 13; depressive type, *n* = 7). Research consensus diagnoses were based on clinical interviews and a semistructured interview by a trained and reliable rater using the Diagnostic Interview for Genetic Studies (Nurnberger et al 1994) that included items from other commonly used instruments (e.g., Structured Clinical Interview for DSM-III-R, patient edition, Spitzer et al 1990; Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms, Andreasen 1983, 1984). Symptom ratings of 60 patients were obtained using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1992). The total Brief Psychiatric Rating Scale (BPRS) score, which was derived from the respective PANSS items, indicated that the patient group was mildly to moderately disturbed (Table 1).

When tested, 52 patients were receiving antipsychotic medications, which were haloperidol (*n* = 18), risperidone (*n* = 9), clozapine (*n* = 8), olanzapine (*n* = 7), fluphenazine (*n* = 3), thiothixine (*n* = 3), perphenazine (*n* = 2), trifluoperazine (*n* = 1), or quetiapine (*n* = 1). The remaining 14 patients (schizophrenic, undifferentiated, *n* = 6; schizophrenic, paranoid, *n* = 4; schizoaffective, bipolar type, *n* = 2; schizoaffective, depressive type, *n* = 2) did not receive antipsychotic medications for at least 14 days before testing.

HEALTHY CONTROL SUBJECTS. Schizophrenic patients were compared with 32 healthy adults (18 male, 14 female) who were recruited from the New York metropolitan area and paid \$10/hour for participation. The ERP data of most control subjects (*n* = 26) have previously been reported (Kayser et al 1998). Control participants were screened using a modified version of

the Schedule for Affective Disorders and Schizophrenia, lifetime version (Spitzer and Endicott 1975) to exclude those with current or past psychopathology. There was no significant difference in mean age between patient and control groups [$F(1,90) < 1.0$], but patients had significantly less education than healthy control subjects [$F(1,90) = 15.1, p = .0002$]. However, education was not significantly associated with either performance or ERP measures in this study.

Stimuli and Procedure

Two auditory target detection (oddball) tasks, using either tonal or phonetic stimuli known to produce opposite perceptual performance asymmetries in dichotic listening studies (e.g., Berlin et al 1973; Sidtis 1981), were chosen to engage participants in predominantly right- or left-lateralized cognitive processing. For the tonal task, stimuli consisted of six square waves with fundamental frequencies between 264 and 485 Hz, corresponding to major notes (C, D, E, G, A, and B) in the octave starting with the middle C. These complex tones had a duration of 250 msec with 25 msec rise and decay time. For the phonetic task, stimuli consisted of three consonant–vowel syllables (/da/, /ta/, /ka/) spoken by a male voice. Syllables had been approximately matched for discriminability, duration, and root mean squared amplitude to the complex tones using STIM software (NeuroScan 1994). All stimuli were presented binaurally at 72 dB sound pressure level via a matched pair of TDH-49 earphones. Earphone orientation and task order were counterbalanced across participants.

Participants listened to a series of either tones or syllables (60 targets and 240 nontargets in each task) in six 50-trial blocks per task with a fixed interstimulus interval of 1750 msec. For the tonal task, each of the six complex tones served once as a target in one block and once as a nontarget in another block. For the phonetic task, each of the three consonant–vowel syllables served as a target twice and was paired with either of the remaining two syllables as the nontarget. Participants were instructed to press a button as quickly as possible after infrequent stimuli (targets). The response hand was the same for both tasks and approximately counterbalanced across participants in each group for each gender (i.e., the left/right press ratios were 8/10 for healthy men, 6/8 for healthy women, 21/22 for schizophrenic men, and 12/11 for schizophrenic women). To reduce ocular artifacts, participants were instructed to fixate a cross on a monitor while listening to the stimuli (for further details, see Kayser et al 1998).

ERP Recording

Electroencephalograms (EEGs) were recorded from 30 standard scalp placements [i.e., four midline (Fz, Cz, Pz, Oz) and 26 paired homologous lateral sites (Fp1/2, F3/4, F7/8, FT9/10, FC5/6, C3/4, T7/8, TP9/10, CP5/6, P3/4, P7/8, P9/10, O1/2)]; for the revised electrode nomenclature of the 10–20 system, see Pivik et al 1993] using a nose reference with an Fpz ground and impedances at 5 k Ω or less. Electroencephalogram gain was 10,000, with a 0.01- to 30-Hz band pass (–6 dB/octave). Data were sampled for 1280 msec at 100 Hz (200 msec prestimulus

baseline) and low pass filtered offline at 20 Hz (-24 dB/octave). Electrooculograms (EOGs) were recorded differentially from the outer canthi of each eye (horizontal bipolar) and from supra- and infraorbital sites (vertical bipolar).

Data Reduction and Analysis

Trials contaminated by artifacts were eliminated when EEG or horizontal EOG data exceeded ± 100 μ V, following vertical EOG reduction (linear regression; Semlitsch et al 1986).¹ For each participant, average ERP waveforms were computed for trials with correct responses for each task (tonal/phonetic) and condition (target/nontarget), resulting in 51.0 (SD = 9.6, range 19–60) and 202.0 (SD = 37.5, range 60–237) trials for control participants and 40.9 (SD = 11.9, range 18–60) and 177.9 (SD = 37.5, range 67–238) trials for schizophrenic patients for targets and nontargets, respectively. Despite the greater loss of trials for patients [$F(1,90) = 11.7, p = .001$], a visual inspection of the ERP waveforms plotted for each subject and each condition revealed that the signal-to-noise ratio was satisfactory in all instances, and the number of valid trials did not differ significantly between tonal and phonetic tasks for either group.

Averaged ERP waveforms were submitted to a tPCA (cf. Picton et al 2000) derived from the covariance matrix, followed by unscaled varimax rotation (for an excellent review of generating ERP measures using PCA methodology, see Chapman and McCrary 1995). As has been previously reported (e.g., Kayser et al 1997, 1998, 1999, 2000), this approach results in the generation of distinctive PCA components (i.e., the factor loadings) and corresponding weighting coefficients (i.e., the factor scores), which more efficiently describe the variance contributions of temporally and spatially overlapping ERP components than conventional ERP measures (e.g., yielding larger effect sizes than mean window amplitudes).² Although several limitations of PCA techniques (e.g., misallocation of variance resulting from latency jitter or component overlap) are well known and demand cautious attention, it is important to recognize that other common ERP measures (e.g., peak or time window amplitudes) are subject to the very same limitations, but unlike PCA, these constraints are never made explicit (e.g., Achim and Marcantoni 1997; Chapman and McCrary 1995; Dien 1998; Möcks and Verleger 1986; Wood and McCarthy 1984). The tPCA was computed using BMDP statistical software (4M; Dixon 1992) for 110 sample points (-100 – 1000 msec) as data matrix columns. Rows consisted of participants (98), tasks (2), conditions (2), and electrode sites (30). The number of orthogonal factors extracted

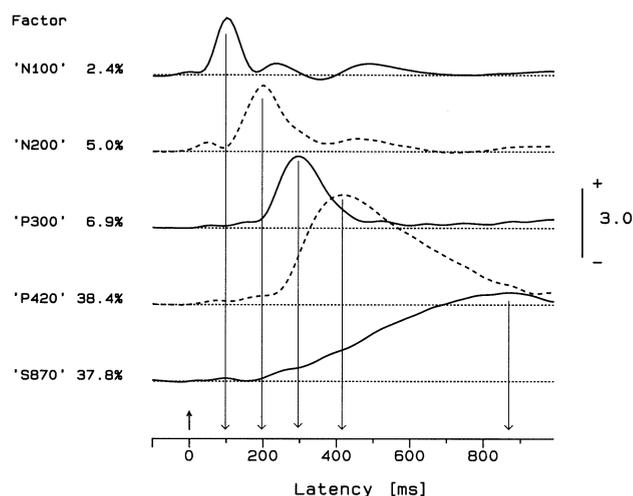


Figure 1. Varimax rotated (unscaled) factor loadings plotted over time for five orthogonal factors extracted by principal components analysis (PCA), ordered by their peak latencies. Factor labels (in single quotation marks) were chosen to reflect both the time course of the factor loadings and the polarity of the associated event-related potential component. Because factor loadings were characterized by low secondary loadings (maximum loadings centered in a narrow time range; cf. Kayser et al 2000), PCA factors may be interpreted as a measure of weighted time window amplitude. Note that the percentage of explained variance largely depends on the time period and the number of electrode locations covered by a factor.

and rotated by the PCA was not limited to maximize the removal of “noise” from meaningful components. Principal components analysis factors were described by the peak latencies of factor loadings and topographies of factor scores. Five principal components, which accounted for 90.5% of the variance after varimax rotation, were considered for further analysis, since they closely corresponded to known ERP components evident in the ERP waveforms (i.e., N1, N2, early P3, late P3, slow wave), and exactly matched factors previously reported for this paradigm (Kayser et al 1998).³

The PCA components are shown in Figure 1, ordered by their peak latencies (for correspondence to ERP waveforms, see Figures 3 and 4). Factor labels (in single quotes) were chosen to reflect the time course (i.e., loadings’ peak latencies) and the polarity of the associated ERP component, which was also inferred from the factor score topographies (cf. Figure 5) mapped for each group, task, and condition. Factor ‘N100’ (2.4% explained variance) peaked at 100 msec and almost entirely

¹ Trials containing blinks during the prestimulus period were eliminated before applying the vertical EOG correction. The effectiveness of the blink correction was validated and, if inadequate, the procedure was reversed, and all trials containing blinks were rejected.

² The interpretation of the extracted PCA components is facilitated by the fact that unscaled, covariance-based, and varimax-rotated factors of ERP waveforms are typically characterized by unique triangle-shaped, positive factor loadings that are 1) clustered in a narrow and coherent time range and 2) lack inverse (negative) or significant secondary loadings at different latencies. The associated factor scores may therefore be interpreted like mean time window amplitudes (i.e., from a time window corresponding to the time interval spanned by the factor loadings), where the center of the time window is given maximum weight, and with gradually lesser weight given to more remote sample points (sample points having zero loadings will not affect the factor score).

³ Separate PCAs were also calculated for patient and control groups, and the resulting time courses of factor loadings and topographies of factor scores were compared to the original overall PCA. Although extraction sequences differed, factors for each group’s PCA closely matched the originally extracted factors for the total sample. Correlations of factor loadings (i.e., over 110 time points for the first 10 factors extracted in each group’s PCA) indicated for each of the five factors included in this report a high correspondence ($.90 \geq r \leq .99$) to precisely one factor extracted from the other group’s data, but negligible correspondence to the remaining factors ($-.57 \geq r \leq .65$). Even higher unique correlations ($.97 \geq r \leq 1.0$) were obtained when factor loadings of each group’s PCA were related to those of the overall PCA, suggesting that these measures are stable and reproducible for different ERP data sets.

overlapped the N1 peak in the ERP waveforms. Analogously, factor 'N200' (5.0% explained variance) peaked at approximately 200 msec and corresponded to the N2 peak. Three factors with amplitude peaks at 300 msec, 420 msec, and 870 msec after stimulus onset accounted for most of the variance in the late positive complex. Factor 'P300' (6.9% explained variance) corresponded to the early phase of a prominent P3 component, and factor 'P420' (38.4% explained variance) to the late phase. A medial–frontal negativity, identified as N3, overlapped the late phase of P3 and was also covered by the time course of factor 'P420.' Finally, factor 'S870' (37.8% explained variance) extended over a relatively long time period at the end of the recording epoch and closely corresponded to a late positive slow wave.

Statistical Analysis

The PCA factor scores for target stimuli were submitted to repeated-measures analysis of variance (ANOVA) with group (patient/control), gender (male/female), and response hand (left/right) as between-subjects factors, and task (syllable/tonal) as a within-subjects factor.⁴ Separate analyses were computed for midline (Fz, Cz, Pz, Oz) and lateral recording sites (13 homologous placements over both hemispheres), adding either one (site) or two within-subjects factors (site and hemisphere) to the design. Guided by our previous findings (Kayser et al 1998), and to increase statistical power for testing *a priori* hypotheses, repeated-measures ANOVAs were conducted for subsets of recording sites at which PCA factor scores were largest and most representative of the associated ERP component. These sites covered midfrontocentral regions for N1 (Fz, Cz, C3/4, F3/4 for factor 'N100'), lateral and medial sites spreading over frontal and parietal regions for N2 (FT9/10, FC5/6, T7/8, C3/4, CP5/6, TP9/10, P7/8, P9/10 for factor 'N200'), and lateral and medial parietal sites for early and late P3 (CP5/6, P3/4, P7/8 for factors 'P300' and 'P420').⁵

Greenhouse–Geisser epsilon (ϵ) correction was used to compensate for violations of sphericity when appropriate (e.g., Keselman 1998; Picton et al 2000). The sources of interactions were systematically examined through simple effects (BMDP-4V; Dixon 1992). Significant group or task differences in component topography were confirmed in separate ANOVAs after vector scaling the amplitudes for each task (i.e., across hemisphere and site; McCarthy and Wood 1985).

To reduce the likelihood of Type I errors given the large sample size, all ANOVA effects were evaluated at a stringent significance level ($p < .01$), which still constituted sufficient statistical power ($f > .98$ for main effects) to detect the medium

to large effects (corresponding to $f > .35$; Cohen 1988) previously reported for healthy adults (Kayser et al 1998). Because repeated-measures ANOVAs were performed on factor scores for a different subset of symmetric electrode placements for each factor (i.e., for sites where PCA factor scores were largest and most representative for the associated ERP component), and to avoid needless complexity, site effects are not reported unless they were particularly relevant.

For analyses of the behavioral data, response latency (mean response time of correct responses), response variability (SD of response latency), and response accuracy (percentage of correct responses to target stimuli) were submitted to repeated-measures ANOVA with group, gender, and response hand as between-subjects factors and task as a within-subjects factor, followed by analyses of simple effects.

For all analyses, gender and response hand were entered as control factors into the ANOVA design, but these variables are not considered further in this report. No significant main effects for gender or task-related topographic interactions with gender were observed in any of the analyses. Effects related to response hand were previously described for healthy adults (Kayser et al 1998) and were similar in patient and control groups.⁶

Pearson correlations were computed to examine the relationship between ERP, behavioral, demographic, and clinical variables. Significant correlations were validated using nonparametric Spearman rank-order correlations.

Results

Behavioral Data

Mean response latency for correct responses was significantly slower for patients (mean = 582.1 msec, SD = 175.2) relative to healthy adults [mean = 470.7 msec, SD = 82.6; group main effect, $F(1,90) = 10.8, p = .002$], and correct responses were slower to phonetic (mean = 573.4 msec, SD = 167.9) than to tonal target stimuli [mean = 518.1 msec, SD = 147.2; task main effect, $F(1,90) = 13.0, p = .0005$]. However, task-related differences in response latency were comparable for patients (tonal = 552.8 msec, SD = 159.6; phonetic = 611.3 msec, SD = 186.1) and control subjects [tonal = 446.4 msec, SD = 80.6; phonetic = 495.1 msec, SD = 78.5; group \times task interaction, $F(1,90) < 1.0$, ns].

Apart from a greater variance in response latency across patients, the individual performance was also less consistent in the patient group. Mean response variability (i.e., the SD of response latency) was 171.4 msec (SD = 77.7) and 217.4 msec (SD = 84.5) for tonal and phonetic tasks for patients and 101.1 msec (SD = 36.6) and 140.4 msec

⁴ The initial ANOVA design also included condition (target/nontarget) as a within-subjects factor, which essentially confirmed that N2 and P3 were present primarily for targets. To reduce the complexity of the design, and to enhance statistical power, effects of interests were evaluated by repeated-measures ANOVA for targets only.

⁵ Similar repeated-measures ANOVAs were performed for factor 'S870,' which characterized the ERPs at a time notably beyond all P3 waveform peaks. Although factor 'S870' was associated with a posterior positive and an anterior negative slow wave, these analyses did not reveal task-related effects (cf. Kayser et al 1998) or particularly meaningful group effects, and were for sake of brevity not included in this report.

⁶ Only a significant group \times response hand interaction emerged in the analysis for factor 'N100' [$F(1,90) = 7.13, p = .009$], stemming from a more robust reduction of N1 amplitude in schizophrenic patients relative to healthy adults for participants responding with their left hand [simple group main effect, $F(1,90) = 37.1, p < .0001$] compared to those responding with their right hand [$F(1,90) = 7.04, p = .009$].

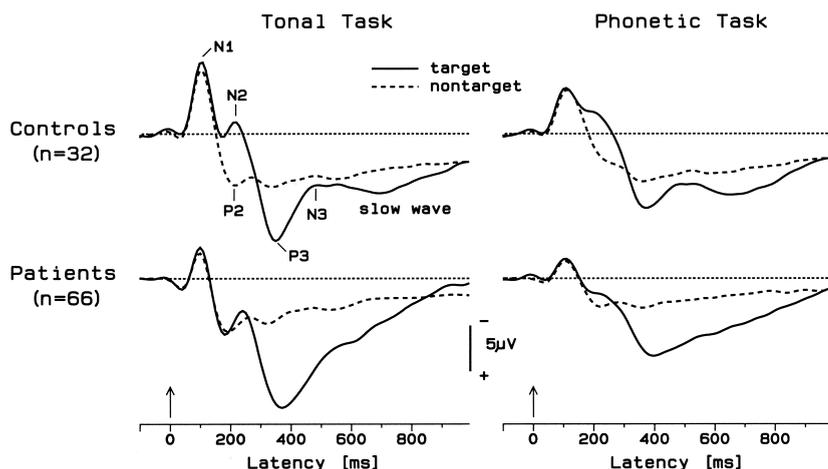


Figure 2. Grand average event-related potential (ERP) waveforms at electrode site Cz (vertex) for 32 healthy adults and 66 schizophrenic patients (averaged across response hand and gender), comparing target and nontarget stimuli for tonal (complex tones) and phonetic (syllables) oddball tasks. Timeline arrows specify stimulus onset. Distinct ERP components (N1, P2, N2, P3, N3, slow wave) are indicated for the control group for the tonal task. Note the marked N2 reduction to target stimuli for patients.

(SD = 43.3) for healthy adults, resulting in significant main effects of group [$F(1,90) = 25.7, p < .0001$] and task [$F(1,90) = 28.0, p < .0001$].

Performance accuracy was high for both groups, but the mean hit rate for patients (mean = 93.0%, SD = 9.2) was significantly lower relative to healthy adults [mean = 98.8%, SD = 4.4; group main effect, $F(1,90) = 10.3, p = .002$]. Accuracy was also lower for the phonetic (mean = 92.3%, SD = 9.9) than the tonal task [mean = 96.8%, SD = 5.4; task main effect, $F(1,90) = 10.2, p = .002$]. Although this analysis revealed a group \times task interaction [$F(1,90) = 5.22, p = .02$] stemming from a lower hit rate to phonetic stimuli than to tonal stimuli for patients [phonetic = 89.9%, SD = 10.8; tonal = 96.1%, SD = 5.9; simple task main effect, $F(1,90) = 22.0, p < .0001$], but not for control subjects [phonetic = 97.2%, SD = 5.1; tonal = 98.3%, SD = 4.9; simple task main effect, $F(1,90) < 1.0, ns$], this effect is likely due to a ceiling effect in the control group.⁷

Average ERP Waveforms and Component Structure

Grand average ERP waveforms for patients and healthy adults in the tonal and phonetic oddball tasks are shown in Figure 2, comparing target and nontarget stimuli at recording site Cz (vertex). Across tasks and groups, distinctive ERP components were identified as N1 (approximate peak latency 100 msec), N2 for targets and P2 for nontargets (220 msec), P3 (between 340 and 420 msec), a relative negative peak for targets labeled N3 (between 460 and 590 msec), and slow wave (beyond 600 msec). Event-related potential waveforms for both groups showed the expected effects of condition—that is, only target stimuli yielded

N2 and P3 amplitudes. However, N2 amplitude was markedly reduced in the patient group across tasks, both in terms of overall potential and in relation to nontarget stimuli.

Grand average ERP waveforms from all 30 recordings for target stimuli are shown for both groups for the tonal and phonetic task in Figures 3 and 4, respectively. Across groups and tasks, N1 was most prominent at frontocentral sites, although smaller for patients and smaller for syllables relative to tones. In control subjects, N2 was most prominent at central and temporal sites for both tasks, and also at parietal sites for the phonetic task, whereas N2 was strikingly reduced in patients across tasks and all sites. P3 and slow wave were broadly distributed over posterior sites in both groups and tasks, with P3 having a maximum over the midparietal region and being larger in the tonal task; no reduction in P3 amplitude was apparent for patients relative to control subjects. N3 was most prominent at frontal–central sites and more evident in healthy adults than in schizophrenic patients.

Findings for PCA Factor Scores

FACTOR N100. As can be seen from Figures 3 and 4, patients had considerably smaller N1 amplitude. This group difference was confirmed by the repeated-measures ANOVA on ‘N100’ factor scores for midfrontocentral (F3/4, C3/4) sites [$F(1,90) = 39.3, p < .0001$] (see also topographic maps in Figure 5). N1 amplitude was also larger for tonal (mean = $-1.25, SD = 1.11$) than for phonetic targets [mean = $-0.54, SD = 0.89$; task main effect, $F(1,90) = 84.0, p < .0001$]. Although this task-related difference was larger for control subjects (tonal = $-2.06, SD = 1.16$; phonetic = $-1.07, SD = 0.77$) than for patients (tonal = $-0.86, SD = 0.84$; phonetic = $-0.28, SD = 0.82$), there was only weak statistical support for a group \times task interaction [$F(1,90) = 5.54,$

⁷ An additional analysis of the sensitivity measure d' , which takes the false alarm rate (less than 2% in both groups) into account, failed to reveal a significant group \times task interaction [$F(1,90) = 1.78, p = .19$] and simply mirrored the group and task main effects observed for response latency.

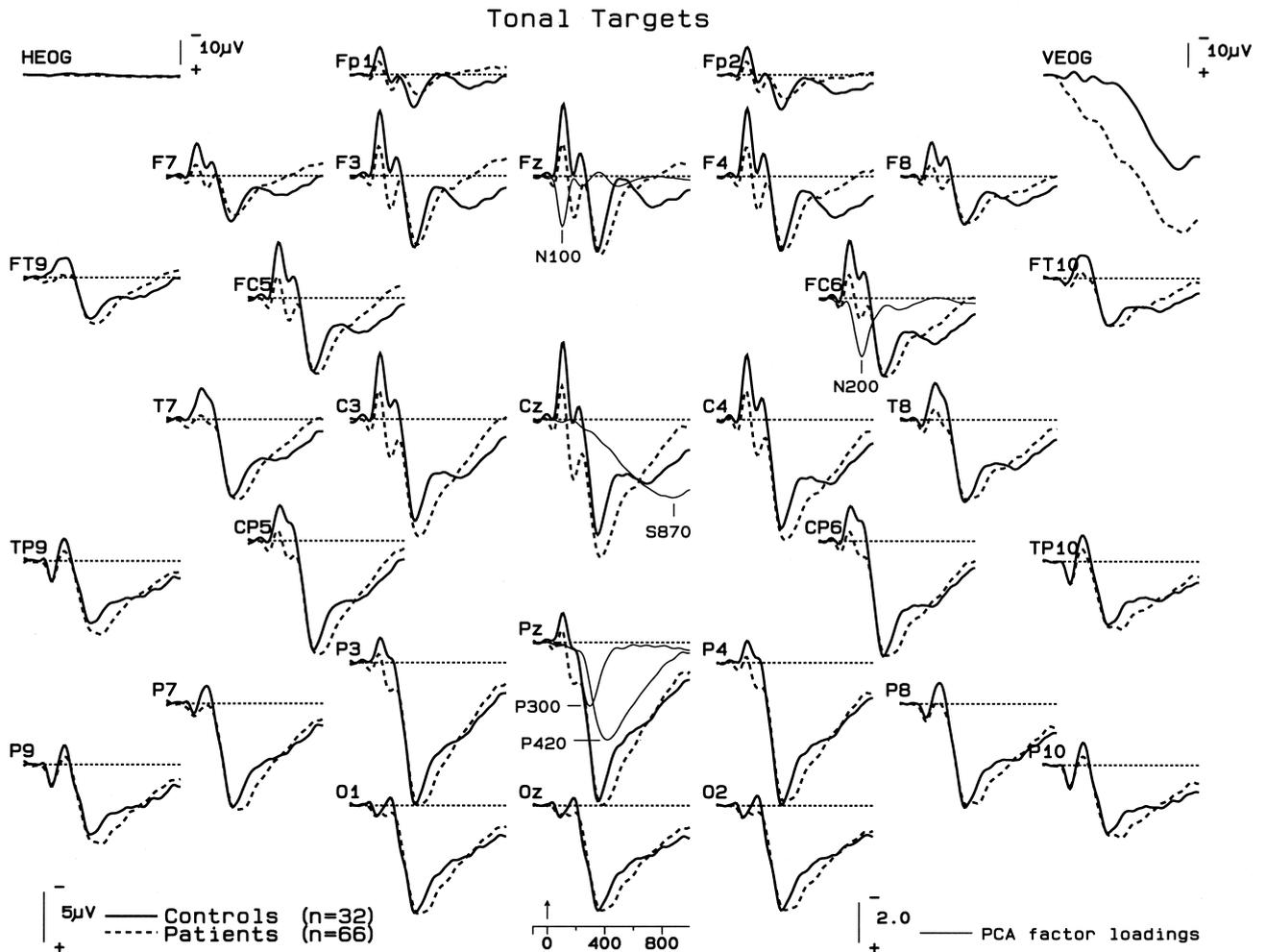


Figure 3. Grand average event-related potential (ERP) waveforms at all 30 recording sites for tonal target stimuli, comparing 32 healthy adults and 66 schizophrenic patients (averaged across response hand and gender). Electrode nomenclature follows the International 10-20 System (Pivik et al 1993), where odd numbers refer to left and even numbers to right hemisphere sites; recording locations covered the whole scalp, spanning from anterior-frontal (Fp1, Fp2) to occipital areas (O1, Oz, O2). Distinct ERP components closely corresponded to the extracted principal components analysis (PCA) factors, as is evident from the time course of the PCA factor loadings (thin solid lines at sites Fz, Cz, Pz, and FC6). Horizontal (HEOG) and vertical (VEOG) electrooculograms are shown at a smaller scale before eye blink correction.

$p = .02$], and simple task main effects were highly significant for both groups [both $F_s(1,90) > 34.0$, both $p_s < .0001$].

FACTOR N200. Patients also showed a smaller N2 amplitude when compared with control subjects, as revealed by the respective ANOVA for lateral and medial sites (FT9/10, FC5/6, T7/8, C3/4, CP5/6, TP9/10, P7/8, P9/10) spanning frontal and parietal regions [$F(1,90) = 53.4$, $p < .0001$] (Figure 5). Interactions of group \times site [$F(7,630) = 15.1$, $p < .0001$, $\epsilon = .24$] and task \times site [$F(7,630) = 23.3$, $p < .0001$, $\epsilon = .30$] were further modified by a group \times task \times site interaction [$F(7,630) = 8.45$, $p = .0003$, $\epsilon = .30$] (Figure 6). Systematic explora-

tion of these interactions by means of simple effects located the largest group differences at more anterior locations for the tonal task (i.e., at FT9/10, FC5/6, C3/4, T7/8, CP5/6), but across lateral-medial sites for the phonetic task [all $F_s(1,90) > 18.5$, all $p_s < .0001$]; however, there was no significant simple group \times task interaction at any site [all $F(1,90)s \leq 3.84$, all $p_s > .05$].

N2 amplitude was larger over the right hemisphere than the left hemisphere for tonal targets, and larger over the left hemisphere than the right hemisphere for phonetic targets [task \times hemisphere interaction, $F(1,90) = 13.5$, $p = .0004$]. As can be seen from Figure 6, these task-dependent N2 asymmetries were more evident for healthy adults than for schizophrenic patients [group \times task \times

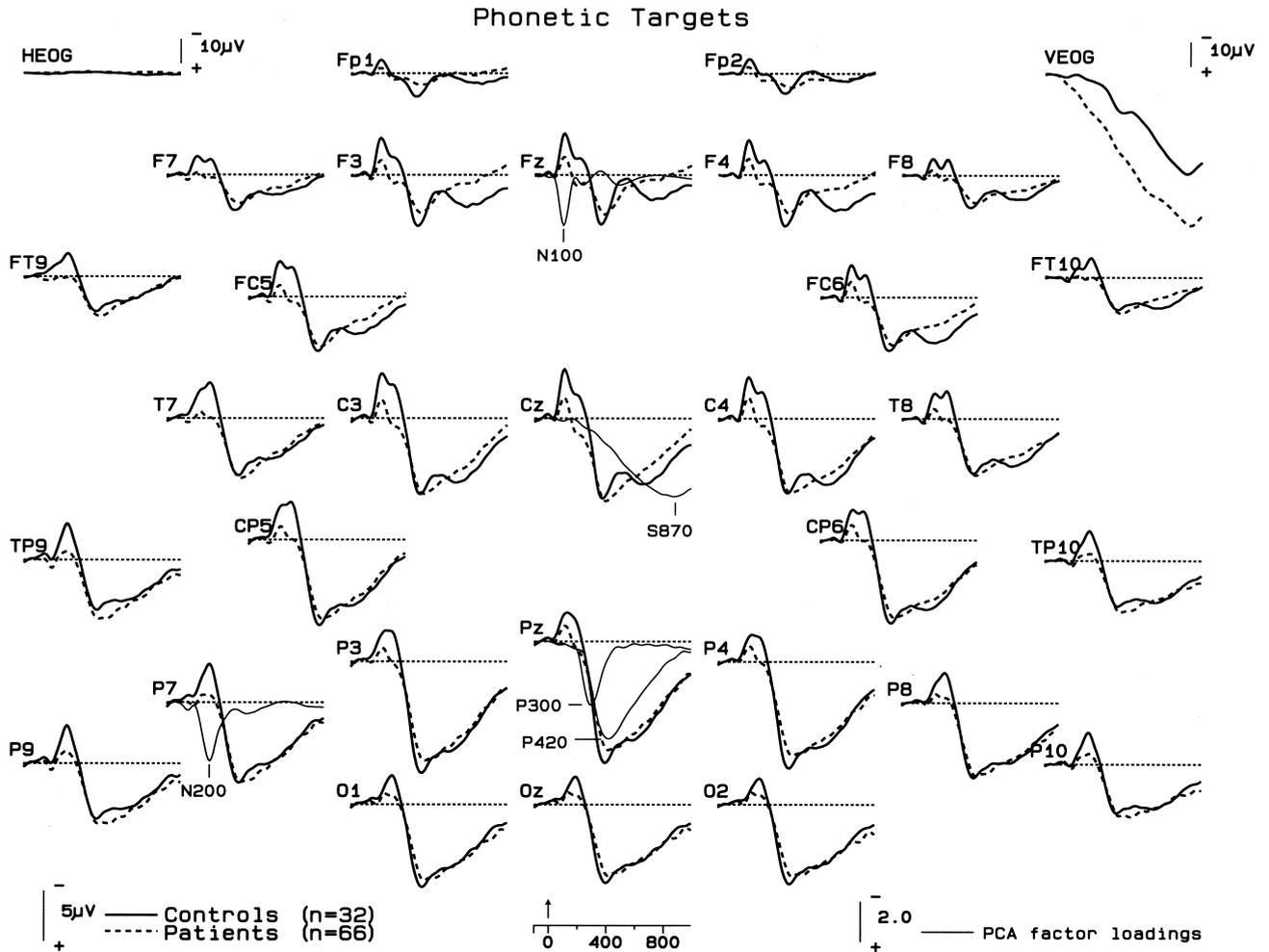


Figure 4. Grand average event-related potential (ERP) waveforms at all 30 recording sites for phonetic target stimuli, comparing 32 healthy adults and 66 schizophrenic patients (averaged across response hand and gender). Distinct ERP components closely corresponded to the extracted principal components analysis (PCA) factors, as is evident from the time course of the PCA factor loadings (thin solid lines at sites Fz, Cz, Pz, and P7). All waveforms are arranged and scaled as in Figure 3.

hemisphere interaction, $F(1,90) = 3.59, p = .06$ [simple task \times hemisphere interactions at control subjects, $F(1,90) = 11.8, p = .0009$; at patients, $F(1,90) = 2.32, p = .13$].

FACTORS P300 AND P420. The classic P3b component seen in oddball tasks (e.g., Squires et al 1975) was represented by two PCA factors with peak loadings at 300 msec and 420 msec that encompassed the P3 waveform peaks for both groups and tasks (see Pz in Figures 3 and 4). Both factors had a maximum amplitude over the midparietal region, which is typical of P3b (Figure 5).

The repeated-measures ANOVA on the factor scores at lateral and medial parietal sites (CP5/6, P3/4, P7/8) revealed task main effects for both factors [for 'P300,' $F(1,90) = 42.0, p < .0001$; for 'P420,' $F(1,90) = 10.7,$

$p = .001$], confirming a greater P3 amplitude for tonal targets than for phonetic targets. For 'P300' amplitude, this task difference was present in both groups [simple task main effects for each group, both $F(1,90) > 16.8$, both $ps \leq .0001$] (Figure 7), whereas a greater tonal than phonetic 'P420' amplitude was found for patients [$F(1,90) = 32.1, p < .0001$] but not for control subjects [$F(1,90) < 1.0$, ns] (Figure 7). The latter effect was the main source for a group \times task interaction for 'P420' amplitude [$F(1,90) = 10.7, p = .001$], but a greater 'P420' amplitude for patients in the tonal task but not the phonetic task also contributed to this interaction [simple group main effect for tonal targets, $F(1,90) = 6.48, p = .01$]. The inverse relation was seen for 'P300' amplitude, revealing a greater 'P300' amplitude for control subjects [group main effect, $F(1,90) = 4.88, p < .03$], particularly in the tonal task [simple group main effect for tonal targets,

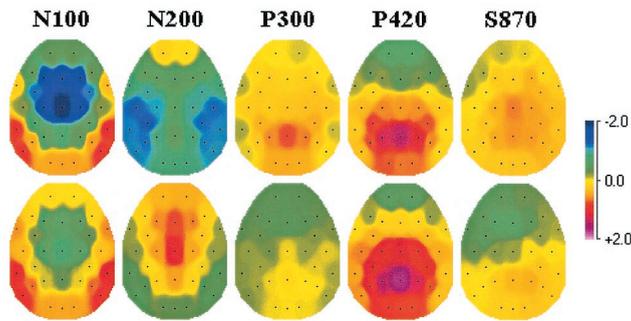


Figure 5. Topographies of principal components analysis (PCA) factor scores at 30 electrode sites (top view, nose upwards) for 32 healthy adults (**top**) and 66 schizophrenic patients (**bottom**) for target stimuli, averaged across task (tonal/phonetic), gender, and response hand. PCA factor amplitudes (from left to right) closely corresponded to event-related potential (ERP) amplitudes of N1 (factor N100), N2 (N200), early P3 (P300), late P3 (P420), and slow wave (S870). Black dots on each map correspond to electrode sites defined in Figures 3 and 4. Maps represent the degree of association of each region with each factor. The sign of the factor scores reflects the polarity of the underlying ERP component (warm colors are associated with positive ERP components, cold colors with negative ERP components). Note that the weights of each component (i.e., the factor scores) reflect the removal of the grand mean ERP waveform for a covariance-based PCA.

$F(1,90) = 5.80, p < .02]$, but this effect alone was insufficient to yield a group \times task interaction for ‘P300’ amplitude [$F(1,90) = 2.86, p = .09]$.

The distinct P3 factors differed in their hemispheric asymmetries (Figure 7). ‘P300’ amplitude was greater across groups over right parietal sites than over left parietal sites for tonal targets [simple hemisphere main effect for tonal targets, $F(1,90) = 12.4, p = .0007]$, and means for the phonetic task were in reverse direction [task \times hemisphere interaction, $F(1,90) = 23.5, p < .0001]$. ‘P420’ amplitude, however, was greater over the left parietal sites than over the right parietal sites across groups and tasks [hemisphere main effect, $F(1,90) = 12.6, p = .0006]$, although this hemispheric asymmetry was more robust for phonetic targets [$F(1,90) = 14.3, p = .0003]$ than tonal ones [$F(1,90) = 6.43, p = .01]$. There was no evidence that the patient and control groups differed in any of these laterality effects.⁸

N2/P3 AMPLITUDE. Because it is generally assumed that N2 and P3 jointly reflect endogenous ERP activity

⁸ To more directly compare our PCA-based findings of P3 amplitude to other studies using conventional ERP measures, mean amplitudes were calculated for a 300–400 msec time window (e.g., Potts et al 1998; Salisbury et al 1998) and submitted to repeated-measures ANOVA as described above. An additional analysis was also performed for this measure selectively at lateral-temporal sites (i.e., T7/8). These time window analyses revealed task and task \times hemisphere effects similar to those found for the PCA factors, but did not show any evidence of left temporal P3 reduction in schizophrenia.

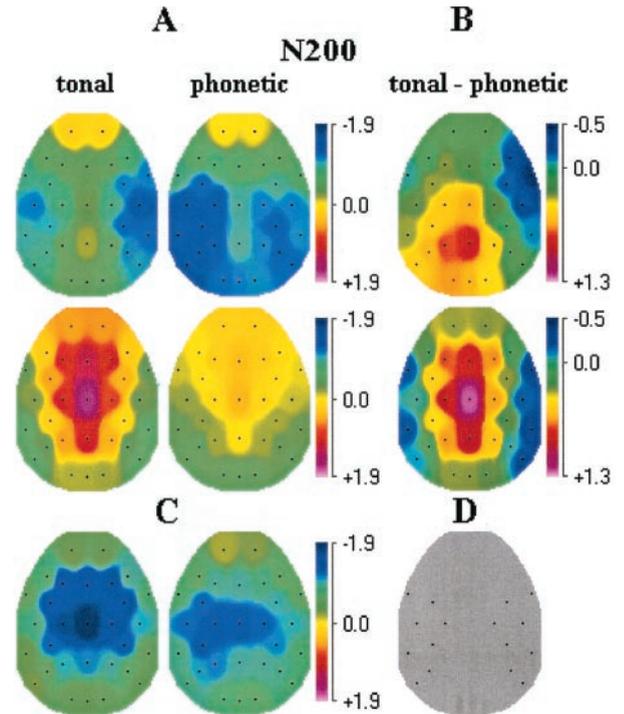


Figure 6. (A) Topographies of principal components analysis factor scores corresponding to N2 for 32 healthy adults (**top**) and 66 schizophrenic patients (**bottom**) for tonal and phonetic target stimuli, averaged across gender and response hand. Negative scores (blue through green colors) are associated with greater N2 amplitude. (B) Corresponding task difference maps (tonal minus phonetic). Negative values (blue shades) indicate greater N2 amplitude for the tonal task. (C) Corresponding group difference maps (control subjects minus patients). Negative values (blue through green colors) indicate greater N2 amplitude for control subjects. (D) Lateral and medial sites spanning frontal and parietal regions (FT9/10, FC5/6, T7/8, C3/4, CP5/6, TP9/10, P7/8, P9/10) used in the statistical analyses for N2.

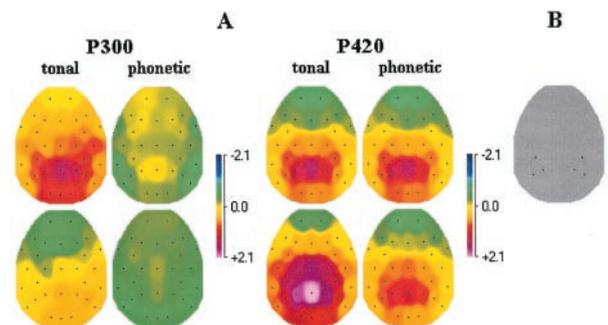


Figure 7. (A) Topographies of principal components analysis factor scores corresponding to early (factor P300) and late (factor P420) P3 for 32 healthy adults (**top**) and 66 schizophrenic patients (**bottom**) for tonal and phonetic target stimuli, averaged across gender and response hand. Positive scores (purple through orange colors) are associated with greater P3 amplitude. (B) Lateral and medial parietal sites (CP5/6, P3/4, P7/8) used in the statistical analyses for early and late P3.

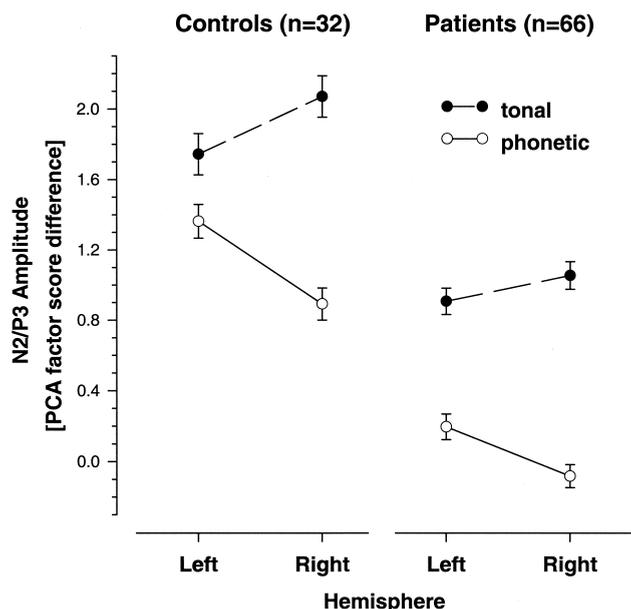


Figure 8. Mean N2/P3 amplitudes (and SEMs) for tonal and phonetic targets at lateral and medial sites of the left (FT9, FC5, T7, C3, CP5, TP9, P7, P9) and right (FT10, FC6, T8, C4, CP6, TP10, P8, P10) hemisphere for the control and patient groups. N2/P3 amplitude was calculated as the difference between principal components analysis (PCA) factor scores of factors corresponding to P3 and N2 ('P300' + 'P420' - 'N200'). Note that the weights of each component (i.e., the factor scores) reflect the removal of the grand mean event-related potential waveform for a covariance-based PCA.

associated with the categorization and evaluation of tonal and phonetic stimuli (e.g., Maiste et al 1995), differences in factor scores representing N2 and P3 were calculated for target stimuli (analogous to N2/P3 peak-to-peak differences). Such estimates of N2/P3 amplitude have been found to be particularly efficient in disentangling task- and condition-related topographic effects from response-related effects (i.e., left- or right-hand button press) because of the capacity of a difference measure to eliminate superimposed, asymmetric response-related negativities that overlay both N2 and P3 (Kayser et al 1998). Since P3 was represented by both factors 'P300' and 'P420,' but to a different degree depending on group, task, and response hand, their sum was used as an overall estimate for P3 amplitude (i.e., 'P300' + 'P420' - 'N200'). These 'N2/P3' factor scores were submitted to the same repeated-measures ANOVA used for factor 'N200.' This analysis revealed significant main effects of group [$F(1,90) = 14.3, p = .0003$] and task [$F(1,90) = 27.1, p < .0001$], stemming from greater amplitudes for healthy adults and for tonal targets relative to phonetic targets. As can be seen from Figure 8, N2/P3 amplitudes were larger over the right hemisphere for tones and larger over the left hemisphere for syllables [task \times hemisphere interaction, $F(1,90) =$

35.5, $p < .0001$], and these task-dependent asymmetries were present for both groups [control subjects, $F(1,90) = 23.1, p < .0001$; patients, $F(1,90) = 12.5, p = .0007$]. These effects can also be seen in the grand mean ERP waveforms by comparing the distance of the N2 and P3 peaks for both groups and tasks (e.g., at sites CP5/6 in Figures 3 and 4).⁹

Relationship between Behavioral Performance and Electrophysiological Measures

The correlations between behavioral and ERP measures were examined separately for both groups and tasks at the most robust recording sites for each ERP component and task (Table 2). As expected, better and more consistent performance was generally associated with larger ERP amplitudes, yielding positive correlations with positive ERP components (early P3, late P3) and negative correlations with negative ERP components (N1, N2). Response latency and variability were inversely related to ERP amplitudes, yielding negative correlations with positive ERP components (early P3, late P3), and positive correlations with negative ERP components (N1, N2). This relationship was particularly evident in patients for N1, N2, and late P3 in the phonetic task; in contrast, control subjects showed this performance link mostly for early P3 in the tonal task. For the phonetic task, a greater N2 amplitude over the left hemisphere relative to the right hemisphere was also moderately associated with higher accuracy in patients ($r = -.29$) and control subjects ($r = -.26$).

Because of the considerable covariation of ERP and behavioral measures, additional analyses of covariance were computed for all ERP measures (BMDP-2V; Dixon 1992). After removal of the three behavioral covariates, the adjusted design means were still highly similar to the original means, but some variance sources were reallocated. Most importantly, group and/or group \times task effects were retained for negative components (i.e., N1, N2). In contrast, the original group main effect for early P3 (reduced amplitude in patients) became insignificant [$F(1,87) = 1.54, p > .21$], and a new group main effect for late P3 (increased amplitude in patients) emerged [$F(1,87) = 8.25, p = .005$].

⁹ N2/P3 amplitude was also analyzed by conventionally defining latency windows for N2 (150–250 msec) and P3 (260–600 msec) and computing the difference of the respective mean voltage areas (i.e., P3 - N2). The results for this measure were in close agreement with those for the PCA-based N2/P3 amplitude, although effect sizes were clearly smaller for the time window measure.

Table 2. Pearson Correlations^a of Behavioral Performance Measures with Event-Related Potential (ERP) Component Measures (Principal Components Analysis [PCA] Factor Scores) for 32 Healthy Adults and 66 Schizophrenic Patients for Tonal and Phonetic Tasks

Variable ^b	ERP component (PCA factor) ^c			
	N1 (N100)	N2 (N200)	Early P3 (P300)	Late P3 (P420)
Healthy adults (<i>n</i> = 32)				
Tonal				
Latency	.31		-.37	-.32
Variability			-.38	
Accuracy	-.29	-.25	.38	
Phonetic				
Latency			-.30	
Variability			-.36	
Accuracy				.25
Patients (<i>n</i> = 66)				
Tonal				
Latency				-.39
Variability		.29		-.38
Accuracy				.38
Phonetic				
Latency	.27	.32		-.53
Variability	.35	.63		-.52
Accuracy	-.36	-.45		.53

^aOnly correlations with $r \geq \pm .25$ are shown, corresponding to a 5% significance level (two-tailed) for 66 patients (for 32 control subjects, $r_{.05} = \pm .29$). Correlations given in boldface indicate a significance level of $p \leq .01$ (two-tailed) for each group.

^bResponse latency (mean response time of correct responses), response variability (SD of response latency), response accuracy (percentage of correct responses to target stimuli).

^cRepresentative means were computed for each PCA factor and task from selected recording sites: for N100, from frontocentral sites (Fz, Cz, F3/4, C3/4); for N200, from lateral sites over the right hemisphere for the tonal task (FT10, FC6, T8, C4, TP10, CP6, P8, P10) and over the left hemisphere for the phonetic task (FT9, FC5, T7, C3, TP9, CP5, P7, P9); for P300 and P420, from parietal sites (Pz, P3/4, P7/8, CP5/6).

Relations to Demographic Variables and Clinical Status

Correlations were also computed across tasks to examine the relation of demographic and clinical variables to behavioral performance and ERP measures. Age was inversely correlated with early P3 amplitude in both groups (for control subjects, $r = -.51$; for patients, $r = -.29$). For patients, a higher total BPRS score was associated with reduced amplitudes of both early ($r = -.26$) and late P3 ($r = -.21$), although the latter correlation was only marginally significant. Likewise, longer illness duration tended to accompany reduced early P3 ($r = -.23$).

Discussion

Distinct ERP components typical of auditory oddball tasks (N1, N2, P3) were clearly evident in both schizophrenic

and control groups during tonal and phonetic tasks. The use of temporal PCA to disentangle temporal and spatial characteristics of these overlapping ERP components not only yielded separate subcomponents of the late positive complex (i.e., early P3, late P3, slow wave), but also provided an improved representation of the different N2 topographies associated with tonal and phonetic discrimination. Similar PCA factors were extracted in both groups, suggesting that these factors are accurate representations of ERP variance during tonal and phonetic oddball tasks (cf. Kayser et al 1998) and not merely artifacts of component latency “jitter” between groups (e.g., Dien 1998; Wood and McCarthy 1984).

Amplitudes of N1, N2, and P3

The most salient abnormality in auditory ERPs of schizophrenic patients in response to complex tones and syllables was a marked reduction of negative potentials (N1, N2) beginning as early as 100 msec after stimulus onset. Similar reductions of early negativities in schizophrenia have been reported for many of these patients in dichotic listening tasks using the same stimuli (Bruder et al 1999), for visual tasks using visuospatial stimuli (Bruder et al 1998) or words (Kayser et al 1999), and for schizophrenic patients in other studies using both auditory and visual discrimination tasks (e.g., Alain et al 1998; Ford et al 1994; O'Donnell et al 1993; Potts et al 1998; Shelley et al 1999; Strandburg et al 1994). This combined evidence strongly indicates that reductions of early negative brain potentials in schizophrenia are not modality, task, or sample specific. The reduction of N1 and N2 amplitude in schizophrenia, respectively, may index a deficit in automatic allocation of attentional and conceptual resources required for categorization of information, although a perceptual processing deficit may also contribute to reductions of N1.

The other remarkable finding of the present study was the preservation of late P3 amplitude in a large sample of schizophrenic patients. This is even more surprising in light of the reduction of earlier negative potentials and poorer performance in patients. Although several studies have failed to demonstrate significant P3 reductions in schizophrenic patients during auditory oddball tasks (Mathalon et al 2000b; Strik et al 1993a, 1997; Weisbrod et al 2000), the reasons for the lack of P3 reduction remain unclear. The present data show that performance level is a crucial variable, as larger late P3 amplitude was associated with better performance among patients. Individual adjustments to equate difficulty levels may in a similar fashion reduce patient-control group P3 differences (Weisbrod et al 2000). The large late P3 amplitude for patients in the present study may reflect their cognitive effort to compen-

sate for an earlier deficit in allocation of attentional or conceptual resources (cf. Bruder et al 1998, but for a discussion on effort and attention as moderators for P3 amplitude in schizophrenia, see also Ford 1999). Such a view would imply that healthy adults and schizophrenic patients employed a different strategy to accomplish successful performance in these target detection tasks. As an alternative interpretation of the reduced early negativities but intact P3, one may question the basic assumption that P3 is entirely dependent upon earlier cognitive processes (e.g., feature extraction, allocation of attention) associated with short latency components (e.g., N1, N2) and instead propose that these components are not generated altogether sequentially but rather in parallel and somewhat independently. As the former hypothesis could be tested in a dual-task paradigm revealing the costs incurred by the patients' additional effort, the alternative interpretation may be regarded as a case in which research with clinical populations can provide information about normal processes.

Several other issues may also account for a preserved late P3 amplitude in the schizophrenic patients. As found here and elsewhere (e.g., Ford et al 1999), P3 amplitude is modulated by clinical severity being smallest in the more ill patients. However, even moderately ill or remitted schizophrenic patients have been found to have some reduction in P3. Nevertheless, the P3 amplitude reported in Ford et al (1999, cf. Figures 2 and 3) for patients having BPRS scores comparable to our patients (i.e., about 30) was close to that seen for healthy control subjects. Similarly, P3 amplitude is inversely related to duration of illness, and therefore the more chronic patients have smaller P3 (Mathalon et al 2000b). Given the slope of the function relating illness duration and P3 amplitude reported by Mathalon et al (2000b, cf. Figure 3), our patients with a mean illness duration of 12 years would be expected to have a normal or close to normal P3 amplitude. However, reduced P3 amplitude has also been found for first-episode patients (Salisbury et al 1998), so chronicity alone is not likely to account for the current findings.

Most patients in this study were receiving atypical antipsychotic medications, but little is known about the effects of these or other drugs on ERP measures. There is some evidence that clozapine treatment leads to cognitive improvements and increased P3 amplitudes (Schall et al 1995; Umbricht et al 1998). Catts et al (1995) reported a reduction in mismatch negativity in schizophrenic patients that was unaffected by their neuroleptic medication status; this short-latency ERP component is automatically elicited during passive listening paradigms and may have contributed to the N1 and N2 effects observed in the present study. In contrast, Roth et al (1991) found smaller N1

amplitudes during active and passive tone stimulation only in medicated patients. Other studies have reported conflicting results as to whether neuroleptic treatment has an effect on ERP measures (e.g., Duncan 1988; Ford et al 1994; Mintz et al 1995; Shagass and Roemer 1991). In general, pre- to posttreatment protocols are hampered by clinical concerns, patient dropout, and small sample sizes, whereas cross-sectional drug studies suffer from between-subjects differences that interfere with the evaluation of medication effects per se (cf. Ford et al 1994). For this sample, the ERPs of 14 unmedicated patients were similar to those of 52 medicated patients and provided no evidence that antipsychotics could produce the marked reductions of N1 or N2 amplitudes or the large P3 amplitudes in patients (Bruder et al, submitted). Further study is needed, however, to determine whether treatment with typical or atypical neuroleptics is associated with ERP changes.

Methodological differences may also generate conflicting findings across studies. Most studies have used an oddball task with very brief pure tones (i.e., 50 msec or less) (e.g., Ford et al 1994; Potts et al 1998; Strik et al 1993b; Weisbrod et al 2000). The present study used tones and consonant-vowel syllables with complex frequency spectra and distinctly longer duration (i.e., 250 msec). Very brief, transient stimuli may be processed differently than longer tones or syllables (e.g., Tallal et al 1998). It is not clear whether or not these stimulus characteristics are critical. However, procedural characteristics have been reported to affect early negativity reductions in schizophrenic patients. During a passive listening paradigm, Shelley et al (1999) found that the patients' deficit in mismatch negativity increased with decreased deviant tone probability, and N1 reductions were more robust with an increased interstimulus interval (ISIs \geq 1000 msec), confirming that N1 generation deficits in schizophrenia are ISI dependent (e.g., Roth et al 1980). Among recording characteristics, the reference electrode is an important issue. We have used a nose reference, whereas most studies have used linked ear lobes or mastoids, or an average reference. To the extent that any reference also shows group or condition effects, such effects are introduced or removed by choice of reference. In the present study, both oddball target/nontarget effects and group differences were clearly evident in an average reference of all 30 EEG channels. Although this observation implies that patient-control group differences may vary across studies using different references, the rereferenced ERPs of this study do not support the idea that reference site could account for the lack of P3 reduction in patients. In any case, the choice of reference cannot account for the lack of P3 asymmetry, since any reference scheme only applies a constant across all electrodes to any sample point in a given ERP waveform.

Task-Related Asymmetries of N2 and P3

The use of both tonal and phonetic oddball tasks in this study allowed us to examine whether schizophrenic patients show task-dependent hemispheric asymmetries of endogenous ERPs. Whereas healthy control subjects showed greater N2 amplitude over right frontotemporal regions for complex tones and over left temporoparietal regions for syllables, these task-dependent asymmetries were less evident in schizophrenic patients. Inasmuch as the N2 asymmetries in healthy adults reflect the differential involvement of cortical networks for automatic pitch or phoneme classification (Kayser et al 1998; Näätänen et al 1997), these automatic processes appear to be impaired in schizophrenia.

Contrary to expectations, however, schizophrenic patients did not show evidence of a specific left-sided deficit. In the tonal oddball task, we did not find the asymmetric P3 reduction seen in some studies (e.g., McCarley et al 1993). Given the correlational findings by Hill and Weisbrod (1999), one could presume that left-lateralized P3 reductions in schizophrenia will be seen only with low overall P3 amplitude. However, a similar post hoc analysis of the present data failed to support this notion, which is in accordance with studies reporting a symmetric P3 reduction in schizophrenic patients (e.g., Ford et al 1994). In a phonetic oddball task, which was designed to preferentially activate left temporoparietal regions, both schizophrenic patients and healthy adults showed greater late P3 amplitude over the left hemisphere. Moreover, patients and control subjects showed opposite, task-dependent hemispheric asymmetries for the tonal and phonetic tasks when N2/P3 differences were examined for PCA factor scores. Thus, schizophrenic patients may display the expected laterality effects for tonal and phonetic oddball tasks, but at a later stage of processing.

Behavioral Performance

Performance accuracy was high for both groups in both oddball tasks (90% hit rate or above), but schizophrenic patients nevertheless performed more poorly than healthy control subjects. Although the poorer performance of patients appeared to be more prominent for the phonetic task, it is likely that this was caused by a ceiling effect in the tonal task. This interpretation is supported by measures of response latency and variability, which indicated that the tonal task was less difficult, and revealed equally poor performance in patients relative to healthy adults in both tasks. Despite the advantage of using simple cognitive tasks that patients can perform, the high accuracy level typically seen in oddball tasks limits the value of these data. More cognitively demanding tasks, such as dichotic listening (Bruder et al 1999) or word recognition memory

tasks (Kayser et al 1999), have provided behavioral and electrophysiological evidence compatible with the hypothesis of a left-lateralized deficit in schizophrenia for language-related processing.

Conclusions

The ERPs of schizophrenic patients were characterized by task-independent reductions of early negativities (N1, N2), spanning a time frame between 80 and 280 msec after stimulus onset, suggesting an early processing deficit in stimulus classification or discrimination. However, the later positive potential, which had a latency of 300 to 550 msec and parietal topography typical of the classical P3b component, was not reduced in patients, suggesting an effortful compensation of an early processing deficit. Although patients' task performance was closely related to amplitudes of N1, N2, and P3, the poorer performance alone could not account for the marked reductions of early negativities. Most notably, task-related hemispheric asymmetries of the N2/P3 complex were similar in healthy adults and schizophrenic patients, suggesting that patients activated the same lateralized cortical networks required for pitch (right frontotemporal) and phoneme (left parietotemporal) discrimination. There was no indication of asymmetric N2 or P3 reductions in patients during either the tonal or the phonetic oddball tasks. Thus, contrary to expectations, schizophrenic patients did not show evidence of a specific left-sided deficit in language-related, phonetic processing. More studies are needed to clarify the role of sample characteristics (e.g., illness severity or chronicity, symptom features, medication status), paradigms (e.g., specific stimulus properties, response requirements), and performance level for ERP abnormalities in schizophrenia.

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References

- Achim A, Marcantoni W (1997): Principal component analysis of event-related potentials: Misallocation of variance revisited. *Psychophysiology* 34:597–606.
- Alain C, Hargrave R, Woods DL (1998): Processing of auditory stimuli during visual attention in patients with schizophrenia. *Biol Psychiatry* 44:1151–1159.

- Alexander JE, Bauer LO, Kuperman S, Morzorati S, O'Connor SJ, Rohrbaugh J, et al (1996): Hemispheric differences for P300 amplitude from an auditory oddball task. *Int J Psychophysiol* 21:189–196.
- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Press.
- Andreasen NC (1983): *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa.
- Andreasen NC (1984): *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa.
- Berlin CI, Hughes LF, Lowe Bell SS, Berlin HL (1973): Dichotic right ear advantage in children 5 to 13. *Cortex* 9:394–402.
- Bruder G, Kayser J, Tenke C, Amador X, Friedman M, Sharif Z, et al (1999): Left temporal lobe dysfunction in schizophrenia: Event-related potential and behavioral evidence from phonetic and tonal dichotic listening tasks. *Arch Gen Psychiatry* 56:267–276.
- Bruder G, Kayser J, Tenke C, Rabinowicz E, Friedman M, Amador X, et al (1998): The time course of visuospatial processing deficits in schizophrenia: An event-related brain potential study. *J Abnorm Psychol* 107:399–411.
- Bruder GE, Kayser J, Tenke CE, Friedman M, Malaspina D, Amador X, et al (submitted): Brain ERPs in schizophrenia during tonal and phonetic oddball tasks: Relations to diagnostic subtype, symptom features and verbal memory.
- Catts SV, Shelley AM, Ward PB, Liebert B, McConaghy N, Andrews S, et al (1995): Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am J Psychiatry* 152:213–219.
- Chapman RM, McCrary JW (1995): EP component identification and measurement by principal components analysis. *Brain Cogn* 27:288–310.
- Cohen J (1988): *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. Hillsdale, NJ: Erlbaum.
- Crow TJ (1997): Schizophrenia as failure of hemispheric dominance for language. *Trends Neurosci* 20:339–343.
- Dien J (1998): Addressing misallocation of variance in principal components analysis of event-related potentials. *Brain Topogr* 11(1):43–55.
- Dixon WJ, editor (1992) *BMDP Statistical Software Manual: To Accompany the 7.0 Software Release*. Berkeley: University of California Press.
- Duncan CC (1988): Event-related brain potentials: A window on information processing in schizophrenia. *Schizophr Bull* 14: 199–203.
- Ford JM (1999): Schizophrenia: The broken P300 and beyond. *Psychophysiology* 36:667–682.
- Ford JM, Mathalon DH, Marsh L, Faustman WO, Harris D, Hoff AL, et al (1999): P300 amplitude is related to clinical state in severely and moderately ill patients with schizophrenia. *Biol Psychiatry* 46:94–101.
- Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994): ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 36:153–170.
- Gruzelier J, Richardson A, Liddiard D, Cheema S, Puri B, McEvedy C, et al (1999): Opposite patterns of P300 asymmetry in schizophrenia are syndrome related. *Int J Psychophysiol* 34:275–282.
- Halgren E, Marinkovic K, Chauvel P (1998): Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalogr Clin Neurophysiol* 106:156–164.
- Hill H, Weisbrod M (1999): The relation between asymmetry and amplitude of the P300 field in schizophrenia. *Clin Neurophysiol* 110:1611–1617.
- Iwanami A, Okajima Y, Kuwakado D, Isono H, Kasai K, Hata A, et al (2000): Event-related potentials and thought disorder in schizophrenia. *Schizophr Res* 42:187–191.
- Javitt DC, Doneshka P, Grochowski S, Ritter W (1995): Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch Gen Psychiatry* 52:550–558.
- Kathmann N, Wagner M, Rendtorff N, Schochlin C, Engel RR (1995): Information processing during eye tracking as revealed by event-related potentials in schizophrenics, alcoholics, and healthy controls. *Schizophr Res* 16:145–156.
- Kay SR, Opler LA, Fishbein A (1992): *Positive and Negative Syndrome Scale (PANSS) Rating Manual*. Toronto: Multi-health System.
- Kayser J, Bruder GE, Friedman D, Tenke CE, Amador XF, Clark SC, et al (1999): Brain event-related potentials (ERPs) in schizophrenia during a word recognition memory task. *Int J Psychophysiol* 34:249–265.
- Kayser J, Bruder GE, Tenke CE, Stewart JW, Quitkin FM (2000): Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: Differences between depressed patients and healthy adults in P3 amplitude and asymmetry. *Int J Psychophysiol* 36:211–236.
- Kayser J, Tenke C, Nordby H, Hammerborg D, Hugdahl K, Erdmann G (1997): Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. *Psychophysiology* 34:414–426.
- Kayser J, Tenke CE, Bruder GE (1998): Dissociation of brain ERP topographies for tonal and phonetic oddball tasks. *Psychophysiology* 35:576–590.
- Keselman HJ (1998): Testing treatment effects in repeated measures designs: An update for psychophysiological researchers. *Psychophysiology* 35:470–478.
- Knight RT (1990): Neural mechanisms of event-related potentials from human lesion studies. In: Rohrbaugh J, Parasuraman R, Johnson R, editors. *Event-Related Brain Potentials: Basic Issues and Applications*. New York: Oxford University Press, 3–18.
- Maiste AC, Wiens AS, Hunt MJ, Scherg M, Picton TW (1995): Event-related potentials and the categorical perception of speech sounds. *Ear Hear* 16(1):68–90.
- Mathalon DH, Ford JM, Pfefferbaum A (2000a): Trait and state aspects of P300 amplitude reduction in schizophrenia: A retrospective longitudinal study. *Biol Psychiatry* 47:434–449.
- Mathalon DH, Ford JM, Rosenbloom M, Pfefferbaum A (2000b): P300 reduction and prolongation with illness duration in schizophrenia. *Biol Psychiatry* 47:413–427.
- McCarley RW, Faux SF, Shenton ME, Nestor PG, Adams J (1991): Event-related potentials in schizophrenia: Their biological and clinical correlates and a new model of schizophrenic pathophysiology. *Schizophr Res* 4:209–231.
- McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R,

- Nestor PG, et al (1993): Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Arch Gen Psychiatry* 50:190–197.
- McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, et al (1999): MRI anatomy of schizophrenia. *Biol Psychiatry* 45:1099–1119.
- McCarthy G, Wood CC (1985): Scalp distributions of event-related potentials: An ambiguity associated with analysis of variance models. *Electroencephalogr Clin Neurophysiol* 62:203–208.
- Menon V, Ford JM, Lim KO, Glover GH, Pfefferbaum A (1997): Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *Neuroreport* 8:3029–3037.
- Mintz M, Hermesh H, Glicksohn J, Munitz H, Radwan M (1995): First month of neuroleptic treatment in schizophrenia: Only partial normalization of the late positive components of visual ERP. *Biol Psychiatry* 37:402–409.
- Möcks J, Verleger R (1986): Principal component analysis of event-related potentials: A note on misallocation of variance. *Electroencephalogr Clin Neurophysiol* 65:393–398.
- Nääätänen R, Lehtokoski A, Lennes M, Cheour M, Huutilainen M, Iivonen A, et al (1997): Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature* 385(6615):432–434.
- NeuroScan (1994): *STIM Software Manual*. Herndon, VA: NeuroScan.
- Nurnberger J, York Cooler C, Kaufmann C, Malaspina D, Harkavy Friedman J, Depaulo JR, et al (1994): Diagnostic interview for genetic studies. *Arch Gen Psychiatry* 51:849–859.
- O'Donnell BF, McCarley RW, Potts GF, Salisbury DF, Nestor PG, Hirayasu Y, et al (1999): Identification of neural circuits underlying P300 abnormalities in schizophrenia. *Psychophysiology* 36:388–398.
- O'Donnell BF, Shenton ME, McCarley RW, Faux SF, Smith RS, Salisbury DF, et al (1993): The auditory N2 component in schizophrenia: Relationship to MRI temporal lobe gray matter and to other ERP abnormalities. *Biol Psychiatry* 34:26–40.
- Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9(1):97–113.
- Pfefferbaum A, Ford JM, White PM, Roth WT (1989): P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. *Arch Gen Psychiatry* 46:1035–1044.
- Pfefferbaum A, Roth WT, Ford JM (1995): Event-related potentials in the study of psychiatric disorders. *Arch Gen Psychiatry* 52:559–563.
- Picton TW (1992): The P300 wave of the human event-related potential. *J Clin Neurophysiol* 9:456–479.
- Picton TW, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson R Jr, et al (2000): Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology* 37:127–152.
- Pivik RT, Broughton RJ, Coppola R, Davidson RJ, Fox N, Nuwer MR (1993): Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology* 30:547–558.
- Potts GF, Hirayasu Y, O'Donnell BF, Shenton ME, McCarley RW (1998): High-density recording and topographic analysis of the auditory oddball event-related potential in patients with schizophrenia. *Biol Psychiatry* 44:982–989.
- Roth WT, Horvath TB, Pfefferbaum A, Kopell BS (1980): Event-related potentials in schizophrenics. *Electroencephalogr Clin Neurophysiol* 48:127–139.
- Roth WT, Goodale J, Pfefferbaum A (1991): Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. *Biol Psychiatry* 29(6):585–599.
- Salisbury DF, O'Donnell BF, McCarley RW, Shenton ME, Benavage A (1994): The N2 event-related potential reflects attention deficit in schizophrenia. *Biol Psychol* 39(1):1–13.
- Salisbury DF, Shenton ME, Sherwood AR, Fischer IA, Yurgelun Todd DA, Tohen M, et al (1998): First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. *Arch Gen Psychiatry* 55:173–180.
- Schall U, Catts S, Chaturvedi S, Redenbach J, Karayanidis F, Ward PB (1995): The effects of clozapine therapy on psychometric and event-related potential (ERP) measures on cognitive dysfunction in schizophrenia. *Schizophr Res* 15:164.
- Semlitsch HV, Anderer P, Schuster P, Presslich O (1986): A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 23:695–703.
- Shagass C, Roemer R (1991): Evoked potential topography in unmedicated and medicated schizophrenics. *Int J Psychophysiol* 10:213–224.
- Shagass C, Straumanis JJ Jr, Roemer RA, Amadeo M (1977): Evoked potentials of schizophrenics in several sensory modalities. *Biol Psychiatry* 12:221–235.
- Shelley AM, Silipo G, Javitt DC (1999): Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: Implications for theories of cortical dysfunction. *Schizophr Res* 37(1):65–79.
- Shelley AM, Ward PB, Catts SV, Michie PT, Andrews S, McConaghy N (1991): Mismatch negativity: An index of a preattentive processing deficit in schizophrenia. *Biol Psychiatry* 30:1059–1062.
- Sidtis JJ (1981): The complex tone test: Implications for the assessment of auditory laterality effects. *Neuropsychologia* 19(1):103–111.
- Spitzer RL, Endicott J (1975): *Schedule for Affective Disorders and Schizophrenia: Lifetime Version*. New York: New York State Psychiatric Institute, Biometrics Research Division.
- Spitzer RL, Williams JBW, Gibbon M, First MB (1990): *Structured Clinical Interview for DSM-III-R—Patient Edition*. Washington, DC: American Psychiatric Press.
- Squires N, Squires K, Hillyard S (1975): Two varieties of long latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalogr Clin Neurophysiol* 38:387–401.
- Strandburg RJ, Marsh JT, Brown WS, Asarnow RF, Guthrie D, Higa J, et al (1994): Reduced attention-related negative potentials in schizophrenic adults. *Psychophysiology* 31:272–281.
- Strik WK, Dierks T, Franzek E, Maurer K, Beckmann H (1993a):

- Differences in P300 amplitudes and topography between cycloid psychosis and schizophrenia in Leonhard's classification. *Acta Psychiatr Scand* 87(3):179–183.
- Strik WK, Dierks T, Maurer K (1993b): Amplitudes of auditory P300 in remitted and residual schizophrenics: Correlations with clinical features. *Neuropsychobiology* 27(1):54–60.
- Strik WK, Fallgatter AJ, Stoeber G, Franzek E, Beckmann H (1997): Specific P300 features in patients with cycloid psychosis. *Acta Psychiatr Scand* 95(1):67–72.
- Tallal P, Merzenich MM, Miller S, Jenkins W (1998): Language learning impairments: Integrating basic science, technology, and remediation. *Exp Brain Res* 123:210–219.
- Tenke CE, Bruder GE, Towey JP, Leite P, Fong R (1993): Behavioral asymmetry for complex tone test (CTT) predicts event-related potential (ERP) asymmetry in an independent oddball task. *Psychophysiology* 30:62–70.
- Tenke CE, Kayser J, Fong R, Leite P, Towey JP, Bruder GE (1998): Response- and stimulus-related ERP asymmetries in a tonal oddball task: A Laplacian analysis. *Brain Topogr* 10:201–210.
- Turetsky B, Colbath EA, Gur RE (1998a): P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change. *Biol Psychiatry* 43:31–39.
- Turetsky BI, Colbath EA, Gur RE (1998b): P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. *Biol Psychiatry* 43:84–96.
- Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, et al (1998): Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry* 44:716–725.
- Weisbrod M, Kiefer M, Marzinzik F, Spitzer M (2000): Executive control is disturbed in schizophrenia: Evidence from event-related potentials in a Go/NoGo task. *Biol Psychiatry* 47:51–60.
- Wood CC, McCarthy G (1984): Principal component analysis of event-related potentials: Simulation studies demonstrate misallocation of variance across components. *Electroencephalogr Clin Neurophysiol* 59:249–260.
- Zipursky RB, Marsh L, Lim KO, DeMent S, Shear PK, Sullivan EV, et al (1994): Volumetric MRI assessment of temporal lobe structures in schizophrenia. *Biol Psychiatry* 35:501–516.