
N1 and P300 Abnormalities in Patients with Schizophrenia, Epilepsy, and Epilepsy with Schizophrenialike Features

Judith M. Ford, Daniel H. Mathalon, Sontine Kalba, Laura Marsh, and Adolf Pfefferbaum

Background: *The scalp-recorded N1 and P300 components of the event-related brain potential (ERP) are commonly reduced in patients with schizophrenia but not in patients with epilepsy. Epilepsy patients with interictal chronic schizophrenialike features (EPI-SZ) provide a comparison group for determining whether the ERP amplitude abnormalities seen in schizophrenic patients are associated with shared clinical features of EPI-SZ and schizophrenic patients or overlapping pathophysiologies, or are specific to a distinct schizophrenia etiology.*

Methods: *Patients with schizophrenia (n = 24) were compared with normal control subjects (n = 32) and patients with epilepsy syndromes on visual and auditory oddball ERP paradigms. Epilepsy patients included those with chronic interictal schizophrenialike features (n = 6) and those without (n = 16).*

Results: *Auditory P300 amplitude was reduced in both schizophrenic and EPI-SZ patients, whose positive or negative symptoms did not differ. In contrast, N1 amplitude was reduced only in schizophrenic patients. Delays in both N1 and P300 were associated with epilepsy patients and EPI-SZ but not schizophrenic patients.*

Conclusions: *The schizophrenialike symptoms in epilepsy probably represent a phenocopy of schizophrenia with common clinical features and some common pathophysiologies but distinct etiologies. P300 amplitude appears to be sensitive to schizophrenialike features, regardless of whether they occur in the context of schizophrenia or epilepsy. N1 amplitude reduction appears to be specific to schizophrenia, suggesting its sensitivity to the distinct etiology of schizophrenia. Biol Psychiatry 2001;49: 848–860 © 2001 Society of Biological Psychiatry*

Key Words: Schizophrenia, epilepsy, P300, N1, psychosis

Introduction

A characteristic neurobiological feature of schizophrenia is reduction in amplitude of the auditory P300 component of the scalp-recorded event-related potential (ERP) (Ford 1999; O'Donnell et al 1999; Pritchard 1986). In cross-sectional analyses, P300 is often reported to vary with negative symptoms (Pfefferbaum et al 1989; Pritchard 1986) and less often with positive symptoms (Ford et al 1999a; McCarley et al 1993). P300 is often smaller in amplitude and longer in latency in patients who have been ill longer (Mathalon et al 2000b). In longitudinal analyses, P300 amplitude is sensitive to fluctuations in the severity of positive symptoms, independent of medication, and to the enduring level of negative symptom severity (Mathalon et al 2000a). Importantly, P300 amplitude reduction also represents a biological trait of the disease, being smaller in schizophrenic patients even in "rigorously defined remission" (Rao et al 1995).

If P300 amplitude reduction persists when the patients are completely free of symptoms, P300 might be an endophenotype of the illness (i.e., a biological marker more proximal to the genes than the overt behavior). Indeed, auditory P300 is reduced in unaffected first-degree relatives of schizophrenics (e.g., Frangou et al 1997). However, its potential utility in diagnosing schizophrenia has been questioned on the basis of its lack of specificity (Roth et al 1984), based mostly on smaller *visual* P300s seen in alcoholics (Porjesz and Begleiter 1993). Modest auditory P300 amplitude reductions have also been associated with major depression (Blackwood et al 1987; Roth et al 1981) and normalize after successful psychopharmacologic treatment (Yanai et al 1997). Others (Salisbury et al 1999) have recently noted that P300 reduction is also seen in manic psychosis, although its scalp distribution differs subtly from that seen in schizophrenia. It is

From the Department of Psychiatry & Behavioral Science, Stanford University School of Medicine, Stanford (JMF, SK), Veterans Affairs Palo Alto Health Care System, Palo Alto (JMF, SK), and SRI International, Menlo Park (DHM, AP), and the Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland (LM). DHM is currently affiliated with the Department of Psychiatry, Yale University, New Haven, Connecticut.

Address reprint requests to Judith M. Ford, Ph.D., VA Palo Alto Health Care System, Psychiatry Research (116F), 3801 Miranda Avenue, Palo Alto, CA 94304.

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important to note that auditory P300 amplitude reduction is not specific to schizophrenia; for example, it is reduced in patients with probable Alzheimer's disease (Ford et al 1997; Polich et al 1990) and in male subjects at high risk for alcoholism (Ramachandran et al 1996; Steinhauer and Hill 1993).

This investigation was undertaken to address the specificity of P300 amplitude reduction to schizophrenia versus other conditions associated with similar clinical features. To this end, we compared patients with schizophrenia to nonschizophrenic but psychotic patients with epilepsy. Approximately 7% of patients with epilepsy develop chronic interictal schizophrenialike psychotic syndromes (Bredkjaer et al 1998; McKenna et al 1985). This led to the suggestion, over 30 years ago (Slater and Beard 1963), that patients with schizophrenia and some patients with epilepsy may share pathogenic processes such as structural brain pathology, that are not directly related to seizure generation. A recent brain imaging study has shown that temporal and extratemporal lobe gray matter deficits, characteristic of patients with schizophrenia, are also seen in patients with epilepsy alone and in patients with epilepsy with schizophrenialike features (Marsh et al 1997a). Although the epileptic patients with schizophrenialike features were not clinically different from the schizophrenic patients, they had greater gray matter volume reductions (Marsh et al 1997b). In addition, patients with epilepsy alone had temporal lobe white matter deficits, as well as smaller hippocampi (Marsh et al 1997a).

In the traditional auditory oddball paradigm, P300 is elicited by an event that is both infrequent and task relevant (Donchin 1981) and may reflect the activity of neural systems subserving novelty detection, effortful attention, and their interaction. Indeed, five overlapping subcomponents of P300 have been identified, reflecting contributions from multiple generators (Turetsky et al 1998). Although the precise neural origins of the scalp-recorded P300 have not been definitively established, studies of patients with well-localized lesions (Woods et al 1987) as well as studies using intracortical recordings have implicated both the temporoparietal junction (Halgren et al 1980; Smith et al 1986, 1990) and regions in the frontal lobes (Halgren et al 1998). It is believed that these separate generators reflect the involvement of different cognitive processes, with temporoparietal generators being more involved in effortful responding and frontal generators being more involved in automatic orienting to infrequent novel or salient stimuli (Ford et al 1994a).

P300s have been recorded from patients with epilepsy both from the scalp (Nelson et al 1991; Puce and Bladin 1991; Soysal et al 1999) and intraoperatively from limbic (Grunewald et al 1999; Puce and Bladin 1991) and frontal lobe (Smith et al 1990) sites. Although the limbic P300 is usually reduced in amplitude or even absent when re-

corded ipsilateral to seizure focus (Grunewald et al 1999; Puce and Bladin 1991), its scalp-recorded counterpart is frequently not reduced in amplitude (Puce and Bladin 1991), perhaps because of the contributions of generators other than those disabled by seizure activity. Though the scalp-recorded P300 is not consistently reduced in epileptic patients, its latency tends to be prolonged to auditory (Puce and Bladin 1991; Triantafyllou et al 1992; Verleger et al 1997) but not visual (Verleger et al 1997) stimuli, possibly related to white matter volume reductions in the temporal lobes of epileptic patients (Marsh et al 1997a).

An earlier, negative component of the ERP, the N1 or N100, is also reduced in amplitude in patients with schizophrenia (Ford et al 1999a; 1994b; Frangou et al 1997; Pfefferbaum et al 1989; Shelley et al 1999; Wagner et al 1996), but not in their first-degree, unaffected relatives (Frangou et al 1997). Although N1 is closely linked with the less-studied P2, they are dissociable experimentally (Ford et al 1976, 1999b; Oades et al 1997), developmentally (Oades et al 1997), and topographically (Roth et al 1976). N1, commonly elicited by simple auditory stimuli, is a composite of at least three identifiable subcomponents (Näätänen and Picton 1987) with generators in temporal (Reite et al 1994, 1988) and frontal lobe structures (Giard et al 1994; Scherg and von Kramon 1986). Although affected by selective attention (Hansen and Hillyard 1983), N1 is also affected by nonspecific arousal (Rockstroh et al 1994; Wagner et al 1996) and is associated with a nonadrenergic metabolite (Ford et al 1994b). Although N1 has been found to be delayed in epileptic patients (Verleger et al 1997), no ERP study to date has reported specifically on patients with epilepsy with schizophrenialike features.

To address whether ERP reflections of schizophrenia are sensitive to neuropathology, etiology, or symptomatology, we compared patients with schizophrenia, patients with epilepsy with schizophrenialike features (EPI-SZ), patients with epilepsy alone, and normal control subjects (NCS). These subjects were drawn from a larger sample (Marsh et al 1997b). All three patient groups shared a common neuropathologic feature, temporal and extratemporal lobe cortical gray matter volume deficits; both epilepsy and EPI-SZ patients shared the common feature of epilepsy, absent in schizophrenia; and EPI-SZ patients shared symptoms of schizophrenia, absent in the epilepsy group.

Methods and Materials

Subjects

Table 1 lists individual subjects and their demographic and clinical characteristics. Table 2 summarizes and compares the demographic and clinical characteristics of these groups. Written

Table 1. Individual Patient Demographics and Clinical Characteristics

Gender	Epilepsy syndrome	Clinical source	Age at test	Years of education	Age at onset of epilepsy (years)	Psychiatric diagnosis
Epilepsy with chronic interictal psychosis (EPI-SZ)						
Male	Partial, nonlocalized	VAHCS	53	13.5	43	Delusional disorder
Male	Partial, nonlocalized	VAHCS	46	12	31	Schizophrenia
Male	Partial, nonlocalized	SCEC	26	12	0.8	Schizophrenia
Male	Generalized	SCEC	32	12	4	Schizophrenia
Male	Temporal, left	VAHCS	33	14	23	Schizophrenia
Male	Primary generalized	SCEC	26	14.5	20	Schizophrenia
Epilepsy without chronic interictal psychosis						
Female	Temporal, right	SCEC	36	14	30	MDD, recurrent
Female	Temporal, right	SCEC	34	14	11	MDD, recurrent
Female	Temporal, right	SCEC	41	14	1.5	Amnesic disorder
Female	Temporal, left	SCEC	43	15	15	None
Female	Temporal, left	SCEC	42	14	4	MDD, recurrent
Female	Temporal, left	SCEC	45	12	10	None
Female	Temporal, left	SCEC	38	17	20	MDD, single episode
Female	Frontal	SCEC	39	13	17	MDD, recurrent
Male	Temporal, right	SCEC	38	18	34	None
Male	Bitemporal	SCEC	42	12	10	GAD
Male	Temporal, right	SCEC	63	19	3	None
Male	Temporal, left	SCEC	51	12	9	Alcohol abuse
Male	Temporal, right	SCEC	42	17	8	None
Male	Frontal, right	SCEC	52	17	19	MDD, single episode
Male	Temporal, left	SCEC	28	14	14	Alcohol abuse
Male	Frontal	SCEC	29	16	20	Bipolar disorder
Schizophrenia						
Male		Napa SH	25	7		Schizophrenia
Male		Napa SH	48	12		Schizophrenia
Male		Napa SH	19	12		Schizophrenia
Male		Napa SH	20	3		Schizophrenia
Male		Napa SH	39	12		Schizophrenia
Male		Napa SH	44	12		Schizophrenia
Male		Napa SH	35	10		Schizophrenia
Male		VAHCS	45	14		Schizophrenia
Male		VAHCS	33	12		Schizophrenia
Male		VAHCS	32	10		Schizophrenia
Male		VAHCS	55	11		Schizophrenia
Male		VAHCS	37	12		Schizophrenia
Male		VAHCS	37	12		Schizophrenia
Male		VAHCS	27	13		Schizophrenia
Male		VAHCS	54	20		Schizophrenia
Male		VAHCS	41	15		Schizophrenia
Male		VAHCS	32	11		Schizophrenia
Male		VAHCS	41	12		Schizophrenia
Male		VAHCS	35	14		Schizophrenia
Male		VAHCS	37	12		Schizophrenia
Male		VAHCS	39	12		Schizophrenia
Male		VAHCS	36	12		Schizophrenia
Male		VAHCS	52	12		Schizophrenia
Male		VAHCS	32	14		Schizophrenia

BPRS, Brief Psychiatric Rating Scale; VAHCS, VA Palo Alto Health Care System; SCEC, Stanford Clinical Epilepsy Center; MDD, major depressive disorder; GAD, generalized anxiety disorder; Napa SH, Napa State Hospital.

informed consent was obtained from all subjects or their guardians.

All subjects were screened, recruited, and assessed using procedures and criteria established by the Stanford/Palo Alto Veterans Administration Mental Health Clinical Research Cen-

ter. Exclusion criteria for all subjects were previous neurosurgery, clinically significant abnormal lab values, severe medical disease, current (<3 months) DSM-III-R/IV diagnosis of alcohol or substance abuse or dependence; alcohol use defined as greater than 80 g on any day within the 2 weeks before the procedure;

Table 1. (Continued)

Age at onset of psychiatric diagnosis	Remote history of alcohol comorbidity	BPRS total (possible range, 18–126)	BPRS Thinking Disorder	BPRS Withdrawal–Retardation	BPRS Anxiety–Depression	BPRS Hostility–Suspiciousness
43	No	27.5	5	4.5	4	7
19	Yes	32	6	7	3	7
24	No	45.5	10	10.5	7	6
31	No	39.5	5.5	13	3.5	7
28	No	37	6.5	10.5	6	6
26	No	43.5	6.5	9	6.5	7.5
17	No	30	4	3	9	6.75
27	No	26	4	3	6	5.5
41	No	19	3	3	3	3
	No	23.5	3	3	5.5	3
39	No	32	3	4	8	7
	No	25.5	3	8	3	3
31	No	31	3.5	3	9.5	5
27	No	24	3	3	3.5	5.5
	No	24	3	3.5	4	4
12	No	31.5	3	3	6.5	5
	No	21	3	3	4	3
19	Yes	29.5	3	3	5.5	5
	No	22	3	3	4.5	3.5
28	Yes	23	3	3	5	3
18	Yes	19	3	3	4	3
23	No	38	3	7.5	13.5	6
14	Yes	37	9	9	4	5
13	No	45	10	10	8	7
14	No	46	9	7	9	10
13	No	49	6	11	5	10
20	No	39	4	10	5	9
29	No	26	3	5	5	6
14	No	50	8	7	8	14
37	No	42	8.5	5	9	8
26	Yes	46.5	9	6.5	10	9.5
17	No	41	8	7	6	9
55	No	37	8	7.5	8	7
19	No	40	8	8	7	7
27	Yes	40	10	6	6	4.5
26	No	54	10	8	9	14
33	No	42	9.5	5	5	8
31	Yes	43	6	10.5	8	8
27	No	40.5	6.5	10.5	9	6
26	No	37.5	6.5	11.5	9	5
25	Yes	35.5	6	12.5	3	8
31	Yes	31.5	4	7	5	5
24	No	47	7.5	11	10	9
20	No	30.5	6.5	4	4	5.5
27	No	52.5	7	7	9	11
18	No	28	6.5	5.5	3	4.5

use of alcohol or illicit drugs within 48 hours of test; or illicit drug withdrawal or drug-related neurologic sequelae within 14 days of procedure. Some subjects in all clinical groups had past histories of alcohol and drug use.

Potential schizophrenic patients and NCS were also screened

and excluded if they had a history of clinically significant head injury (loss of consciousness of >30 min and/or with neurologic sequelae) or other central nervous system disease.

Psychiatric diagnoses were based on a clinical interview by a clinician investigator and a structured interview (Structured

Table 2. Subject Demographics and Clinical Characteristics (Means and SDs)

Group	Age	Years of Education	Handedness (right, 14– 32; left, 50–70)	Length of illness primary diagnosis	Age at onset of primary diagnosis	BPRS total	BPRS Thinking Disorder	BPRS Withdrawal– Retardation	BPRS Anxiety– Depression	BPRS Hostility– Suspiciousness
Normal control subjects F, 7; M, 25	38 (7.9)	16 (2.8)	27.7 (16.1)	—	—	—	—	—	—	—
Epilepsy F, 8; M, 8	41.4 (8.7)	15 (2.2)	21.9 (13.8)	27.3 (14.9)	14.1 (9.1)	26.2 (5.3)	3.2 (0.4)	3.7 (1.6)	5.9 (2.8)	4.5 (1.4)
Epilepsy with schizophrenialike features (EPI-SZ) M, 6	34.7 (10.7)	12.7 (1.3)	19.3 (6.8)	14.3 (9.0)	20.4 (14.6)	37.4 (6.2)	6.5 (1.6)	8.3 (3.5)	6 (3.1)	6.7 (0.6)
Schizophrenia M, 24	37.3 (9.3)	11.9 (3.0)	17.6 (3.6)	(13.2) (8.0)	24.4 (9.4)	40.9 (7.3)	7.4 (1.9)	7.9 (2.4)	6.9 (2.2)	7.8 (2.7)

BPRS, Brief Psychiatric Rating Scale;

Clinical Diagnostic Interview—Patient Version; SCID-P) (Spitzer et al 1992) or SCID-P—Epilepsy Version (J. Victoroff et al, unpublished data) administered by a trained research assistant and established by consensus using criteria from DSM-III-R/IV.

Severity and intensity of psychopathology in patients were assessed with the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) administered by two trained raters, and the average of both ratings was used. Individual item scores were clustered to yield four factor scores that reflect Thinking Disturbance (hallucinatory behavior, unusual thought content, conceptual disorganization), Hostility–Suspiciousness (suspiciousness, hostility, uncooperativeness), Withdrawal–Retardation (blunted affect, emotional withdrawal, motor retardation), and Anxiety–Depression (anxiety, depressed mood, guilt feelings) (Hedlund and Vieweg 1980; Overall et al 1967). Thinking Disturbance and Withdrawal–Retardation scores were used to assess positive and negative symptoms, respectively.

Patients with epilepsy were recruited from the Stanford Comprehensive Epilepsy Center. All had simple or complex partial seizures with or without secondary generalization that had been electrographically localized, had unsatisfactory seizure control despite trials with multiple antiepileptic medications (range, two to 10 different medications), and were candidates for neurosurgical resection. None had a chronic interictal psychotic syndrome.

Patients with epilepsy with chronic interictal schizophrenialike syndromes were recruited from the inpatient and outpatient facilities of the Stanford Comprehensive Epilepsy Center and the VA Palo Alto Health Care System. This group included patients with epilepsy who, between seizures, manifested the phenomenology of chronic schizophrenia or chronic delusional disorder, based upon DSM-III-R/IV criteria. Epilepsy patients with schizoaffective disorder, psychotic affective disorder, transient psychotic syndromes in the context of postictal episodes, delirium, status epilepticus, drug toxicity or withdrawal, or mental retardation, or patients with schizophrenia who experienced medication-related to alcohol withdrawal seizures were not included. In addition to seizure medications, all but one patient were taking typical or atypical antipsychotic medications at the time of ERP testing.

Patients with schizophrenia who met DSM-III-R/IV criteria for chronic schizophrenia were drawn from inpatient psychiatric wards at the VA Palo Alto Health Care System and Napa State Hospital to match the epilepsy and EPI-SZ subjects in age. They were all medicated with either typical or atypical antipsychotic medications at the time of ERP test. Data from these groups have been previously reported (Ford et al 1994b, 1999a; Mathalon et al 2000a, 2000b).

Normal control subjects were men ($n = 25$) and women ($n = 7$) without current or past major medical or psychiatric illnesses (based on SCID interviews), selected from a pool of healthy subjects who had previously served as control subjects for ERP studies of schizophrenia and alcoholism, to match the age and gender composition of the EPI-SZ and epilepsy-alone groups. Subjects who responded to recruitment advertisements were initially screened over the phone. Those passing this screen and willing to participate were invited to the laboratory, where they were further screened by a psychiatric interviewer using the

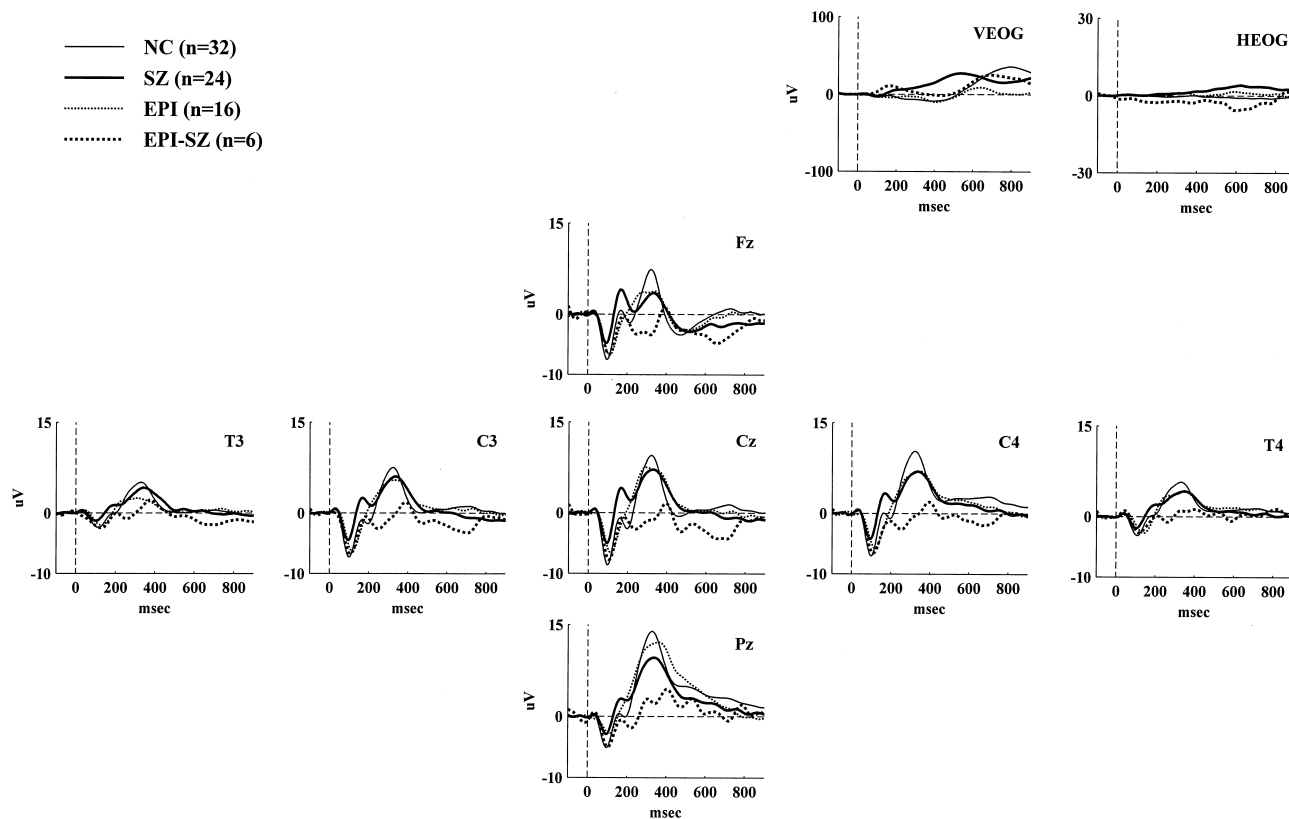


Figure 1. Grand average event-related potentials (ERPs) elicited by target tones during the Effortful Auditory paradigm are overlaid for the four groups. VEOG and HEOG activity have been removed from the ERPs, but are shown here for illustrative purposes. NC, normal control subjects; SZ, schizophrenic patients; EPI, epilepsy patients; EPI-SZ, epilepsy patients with interictal chronic schizophrenialike features. VEOG, vertical electro-oculogram; HEOG, horizontal electro-oculogram.

Schedule for Affective Disorders and Schizophrenia—Lifetime (Endicott and Spitzer 1978).

ERP Recording

Data were collected using the following ERP paradigms in the order described.

EFFORTFUL AUDITORY PARADIGM. Subjects wore earphones, sat upright in an easy chair in a sound-attenuated room, and were presented with 400 auditory stimuli at a fixed inter-stimulus interval of 1.5 seconds. Frequent tones (500 Hz, 80 dB sound pressure level, 50-msec duration with a shaped 5-msec rise and fall time) occurred on 80% of the trials. Infrequent target tones (1000 Hz, 80 dB sound pressure level, 50 msec) occurred on 20% of the trials in a Bernoulli sequence held constant across subjects. Subjects were asked to press a reaction time button, with the preferred hand, to the target stimuli only, giving equal importance to speed and accuracy.

EFFORTFUL VISUAL PARADIGM. This paradigm is a visual version of the effortful auditory paradigm, in which stimuli appeared on a cathode ray tube. Minus signs appeared on 80% of the trials, and plus signs (targets) appeared on the other 20%.

Stimulus duration was 200 msec. As in the effortful auditory paradigm, subjects were asked to press a reaction time button, with the preferred hand, to the target stimuli only, giving equal importance to speed and accuracy.

Event-related potentials recorded from Fz, Cz, Pz, T3, C3, C4, T3, and T4, referenced to linked mastoids (A1 and A2), are shown in Figures 1 and 2. Vertical electro-oculograms (EOGs) were recorded from electrodes placed above and below the right eye, and horizontal EOGs from electrodes placed at the outer canthi of each eye. Impedances were below 5 k Ω . Data were sampled every 5 msec and epoched with a 100-msec prestimulus baseline to 1150 msec poststimulus. Single trials from each electrode site were subjected to the following computer-based procedures: 1) trials with button presses occurring before 100 msec or after 1150 msec were excluded, as were those with incorrect button presses; 2) trials were excluded if an electroencephalogram (EEG) at any electrode site exceeded $\pm 250 \mu\text{V}$; 3) trials were individually corrected for the effects of eye blinks and eye movements (Gratton et al 1983; Miller et al 1988); 4) for each trial, a 100-msec prestimulus baseline was subtracted from the poststimulus activity; and 5) single trials with movement or artifacts ($> \pm 200 \mu\text{V}$) were excluded. Remaining corrected trials were averaged to form ERPs. Before peak identification, ERPs were filtered with a 0.5-Hz (down 3 dB) high-pass filter

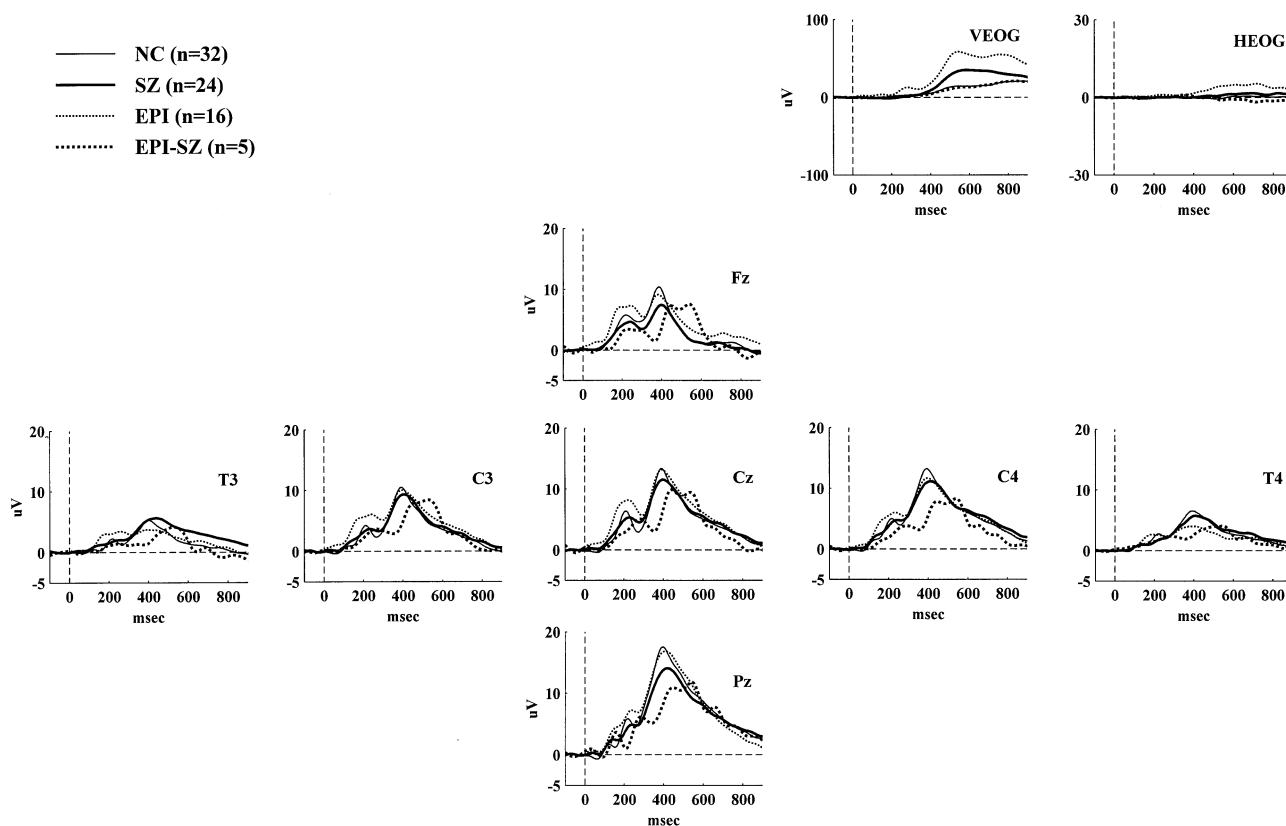


Figure 2. Grand average event-related potentials (ERPs) elicited by visual targets during the Effortful Visual paradigm are overlaid for the four groups. VEOG and HEOG activity have been removed from the ERPs, but are shown here for illustrative purposes. NC, normal control subjects; SZ, schizophrenic patients; EPI, epilepsy patients; EPI-SZ, epilepsy patients with interictal chronic schizophrenialike features. VEOG, vertical electro-oculogram; HEOG, horizontal electro-oculogram.

(Coppola 1979) and with a 12.4-Hz (down 3 dB) low-pass filter (Ruchkin and Glaser 1978). Event-related potentials to targets recorded from seven scalp sites are plotted in Figure 1 for the Effortful Auditory paradigm and in Figure 2 for the Effortful Visual paradigm. Correct reaction times (RTs) and numbers of accurate target detections were tallied, independent of EEG exclusion criteria.

The following peaks were identified by computer algorithm: N1 to target and frequent auditory events was identified as the most negative peak between 50 and 200 msec, and P300 to auditory and visual target events was identified as the most positive peak between 280 and 800 msec at all scalp sites. In two cases, visual inspection revealed that the computer algorithm failed to identify P300, and more restrictive windows were used.

Statistical Analyses

Event-related potential amplitudes and latencies (N1 at Cz and P300 at Fz and Pz) as well as RT and accuracy data, were analyzed in nonparametric tests due to the small and uneven sample sizes. Kruskal–Wallis analyses of variance were used to identify effects of Group on amplitude and latency, followed by Mann–Whitney *U* tests, corrected for ties. Clinical symptoms were compared between the schizophrenic and EPI-SZ patients using the Mann–Whitney *U* tests. To understand differences in

ERP values between these groups, ERP amplitudes and latencies were correlated with clinical symptoms using Spearman non-parametric correlation analyses. Data from epilepsy patients could not be considered in these analyses because of their low scores and lack of variance on clinical symptom scales.

Results

Clinical Symptoms

Schizophrenic patients and EPI-SZ patients did not differ in positive symptoms (Thinking Disturbance, $z = 1.20$, $p = .23$) or negative symptoms (Withdrawal–Retardation, $z = 0.83$, $p = .40$), although there was a tendency for schizophrenic patients to have more symptoms of Anxiety–Depression ($z = 1.75$, $p < .08$).

Reaction Time and Response Accuracy

Reaction time in both auditory [$H(3,78) = 10.95$, $p < .012$] and visual [$H(3,78) = 12.20$, $p < .007$] paradigms was affected by Group. In both modalities, RT was longer in both schizophrenic (auditory, $z = 2.09$, $p = .04$; visual, $z = 2.77$, $p = .006$) and EPI-SZ

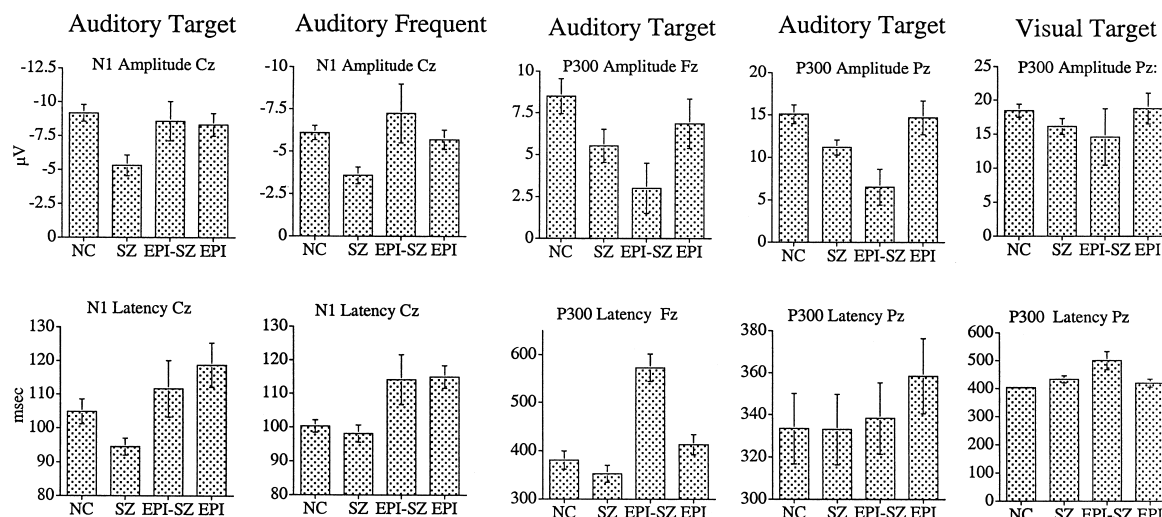


Figure 3. Means and SEMs for N1 amplitude and latency to target and frequent auditory stimuli, and P300 amplitude and latency to target visual stimuli at Pz and target auditory stimuli at Fz and Pz for normal control subjects (NC) and patients with schizophrenia (SZ), epilepsy with schizophrenialike features (EPI-SZ), and epilepsy (EPI). Standard errors for Visual P300 in NC are too small to be displayed at scale used for this figure.

(auditory, $z = 2.95$, $p = .003$; visual, $z = 2.58$, $p = .01$) patients than NCS. Epilepsy patients showed RT deficits relative to NCS only in the auditory paradigm ($z = 2.056$, $p = .04$).

Accuracy (percent correct) was affected by group for the auditory [$H(3,78) = 9.57$, $p = .023$] and visual [$H(3,78) = 7.78$, $p = .05$] paradigms. For the auditory paradigm, both EPI-SZ ($z = 3.49$, $p = .0005$) and schizophrenic ($z = 2.03$, $p = .043$) groups were less accurate relative to NCS. For the visual paradigm, only the schizophrenic group was less accurate than NCS ($z = 2.27$, $p = .024$).

Auditory N1 Amplitude and Latency

N1 amplitude to the target event was affected by Group [$H(3,78) = 13.84$, $p < .004$] (Figures 1 and 3). Pairwise comparisons revealed that schizophrenic patients had smaller N1s than NCS ($z = 3.49$, $p < .0005$) who did not differ from epilepsy ($z = 0.77$, $p = .44$) or EPI-SZ ($z = 0.28$, $p = .78$) patients. Results for N1 amplitude to frequent tones paralleled those for N1 to the target, with a significant Group effect [$H(3,78) = 15.10$, $p < .002$] and follow-up tests indicating that N1 was reduced only in schizophrenic patients ($z = 3.59$, $p < .0003$) but not in EPI-SZ ($z = 0.52$, $p = .60$) or epilepsy ($z = 0.24$, $p = .81$) patients. Within schizophrenic patients, larger Withdrawal-Retardation scores were associated with smaller N1s (larger positive values) to both target tones ($\rho = .43$, $p < .04$) and frequent tones ($\rho = .78$, $p < .0002$). N1 was not related to positive

symptoms as measured by Thinking Disturbance (targets, $\rho = .12$, $p = .55$; frequent, $\rho = .14$, $p = .47$).

N1 latency to the target event was also affected by Group [$H(3,78) = 16.66$, $p < .0008$] (Figure 3). Pairwise comparisons revealed that schizophrenic patients had earlier N1s than NCS ($z = 2.47$, $p < .02$), but that N1 was delayed in epilepsy patients ($z = 2.59$, $p = .01$), with no delay in EPI-SZ patients ($z = 0.96$, $p = .33$). Results for N1 latency to frequent tones showed a somewhat different pattern of effects [$H(3,78) = 17.47$, $p < .0006$]; N1 was later in both epilepsy ($z = 3.35$, $p < .0008$) and EPI-SZ ($z = 2.08$, $p < .04$) patients but was not earlier in schizophrenic patients ($z = 0.95$, $p = .34$). Neither the slowing of N1 latency in EPI-SZ patients nor its speeding in schizophrenic patients were related to symptomatology.

Auditory P300 Amplitude and Latency

In the auditory paradigm, P300 amplitude at Pz was affected by Group [$H(3,78) = 13.57$, $p < .004$] (Figures 1 and 3). Relative to NCS, P300 was reduced in EPI-SZ ($z = 3.04$, $p < .003$), schizophrenic ($z = 2.5$, $p < .02$), but not epilepsy ($z = 0.12$, $p = .90$) patients. P300 was smaller in EPI-SZ than in schizophrenic patients ($z = 1.97$, $p < .04$). Amplitude reduction in the schizophrenic and EPI-SZ patients was not related to either positive or negative symptoms. However, in the schizophrenic patients considered separately, smaller P300 amplitudes were related to more

Withdrawal–Retardation ($p = .42, p < .04$) but were not related to Thinking Disturbance ($p = .11, p = .60$).

P300 latency at Pz was also affected by Group [$H(3,78) = 8.30, p < .04$], being delayed in epilepsy ($z = 3.10, p = .002$) but not in schizophrenic ($z = 0.47, p = .64$) or EPI-SZ ($z = 0.12, p = .90$) patients.

P300 at Fz was also affected by Group [$H(3,78) = 7.81, p = .05$] (Figures 1 and 3). Relative to NCS, the frontal P300 was reduced in EPI-SZ ($z = 2.32, p = .02$), schizophrenic ($z = 2.00, p < .05$), but not epilepsy ($z = 0.59, p = .55$) patients. The frontal P300 was not significantly smaller in EPI-SZ than in schizophrenic patients ($z = 1.35, p = .18$). Amplitude reduction of the frontal P300 in the schizophrenic and EPI-SZ groups was not related to symptoms.

P300 latency at Fz was also affected by Group [$H(3,78) = 12.05, p = .007$], being delayed in EPI-SZ ($z = 3.09, p = .002$) but not in schizophrenic ($z = 0.76, p = .45$) or epilepsy ($z = 1.44, p = .15$) patients relative to NCS.

Visual P300 Amplitude and Latency

In the visual paradigm, P300 amplitude was not affected by Group [$H(3,77) = 4.87, p = .18$], but P300 latency was [$H(3,77) = 13.37, p < .004$] (Figures 2 and 3). In contrast to the auditory P300 latency, visual P300 was not delayed in epilepsy patients ($z = 1.63, p = .10$) but was delayed in EPI-SZ patients ($z = 3.34, p < .0008$). It was marginally delayed in schizophrenic patients ($z = 1.96, p = .05$). These delays were not related to either positive or negative symptoms.

Discussion

To address whether ERP reflections of schizophrenia are sensitive to etiologic, clinical, or pathophysiologic factors, we compared schizophrenia, epilepsy, and EPI-SZ patients. Epilepsy and EPI-SZ patients shared the common phenomenon of seizures not seen in schizophrenia, whereas schizophrenic and EPI-SZ patients shared common psychiatric features, not seen in epilepsy patients. However, all three shared common cortical gray matter volume reductions (Marsh et al 1997a, 1997b). We found P300 amplitude reductions in both EPI-SZ and schizophrenic patients, but not in epilepsy patients, suggesting P300 reduction may be sensitive to schizophrenialike features, but not to the common cortical gray matter volume reductions. In contrast, N1 reduction is specific to schizophrenia patients, suggesting its sensitivity to non-clinical, perhaps etiologic, aspects of the illness.

Because both schizophrenic and EPI-SZ patients had

reductions in P300, it is important to consider what variables besides schizophrenialike features these two groups had in common. Both were taking antipsychotic medications. Although the P300 reduction common to both groups could be the result of these medications, this is unlikely (Ford et al 1994b; Mathalon et al 2000a). Indeed, since antipsychotic medication is expected to improve clinical state, and P300 generally also improves with improvements in clinical state (Mathalon et al 2000a), a medication effect, if any, would be associated with increased rather than decreased P300 amplitude. Furthermore, illness duration is unlikely to explain P300 amplitude reduction in EPI-SZ relative to epilepsy patients because longer duration of illness is associated with smaller P300s (Mathalon et al 2000b) and EPI-SZ patients have shorter illness duration (16 years) than epilepsy patients (27 years). The antiseizure medications taken by the EPI-SZ patients are unlikely to have caused the P300 amplitude reduction because the epilepsy patients were on the same medications and did not demonstrate a similar reduction.

We have shown that cortical gray matter volumes contribute to P300 amplitude in healthy control subjects (Ford et al 1994a) and that P300 reductions in schizophrenia can partially, but not entirely, be explained by cortical gray matter volume reductions (Ford et al 1996). Although temporal lobe gray matter volume reductions common to both schizophrenic and EPI-SZ patients might contribute to P300 amplitude reductions, it is unlikely to be a major factor. Epilepsy and schizophrenic patients have similar gray matter volume reductions (Marsh et al 1997a, 1997b), yet schizophrenic patients had greater P300 amplitude reductions. Furthermore, EPI-SZ patients had greater cortical gray matter volume reductions than schizophrenic patients (Marsh et al 1997b), perhaps contributing to the greater reduction in P300 in the EPI-SZ patients.

The EPI-SZ group had levels of both positive and negative symptoms comparable to those of the schizophrenic group, making it hard to determine which clinical features contributed to the observed reductions in P300 amplitude in both groups. Although cross-sectional data often show that P300 amplitude reduction is associated with negative symptoms in schizophrenia, a recent longitudinal study has also shown within-subject fluctuations in positive symptoms over time to covary with P300 amplitude variation (Mathalon et al 2000a). Because negative symptoms tend to be more enduring than positive symptoms, which fluctuate more over time (Johnstone et al 1986; Mathalon et al 1999; Mueser et al 1991; Pfohl and Winokur 1982; Pogue-Geile and Harrow 1985; Putnam et al 1996), cross-sectional correlations are more likely to be detected between P300 amplitude and negative symptoms than between P300 amplitude and positive symptoms, as

was the case for schizophrenic patients in this study. However, the lack of correlation between positive symptoms and P300 amplitude in our sample does not preclude a role for positive psychotic symptoms, and/or their underlying neurophysiologic mechanisms, in the reduction of P300 amplitude in both psychotic patient groups. It appears that the schizophrenialike syndrome present in the epilepsy patients was essentially indistinguishable from current symptom-based definitions of schizophrenia with respect to P300 amplitude deficits.

To the extent that women have larger P300s than men (Polich and Hoffman 1998), the lack of women in the schizophrenic and EPI-SZ groups may also have contributed to their P300 reduction. To address this possibility, we compared EPI-SZ to epilepsy patients, with and without women in the sample. Mean P300s in the epilepsy group were 14.67 μ V with women and 13.79 μ V without women, and in both cases larger than in the EPI-SZ group [with women, $F(1,20) = 5.409$, $p = .03$; without women, $F(1,12) = 5.59$, $p < .04$]. Thus the uneven gender composition of groups in this sample probably does not contribute to the effects observed.

In contrast to P300 amplitude deficits, N1 amplitude deficits were only observed in the schizophrenic group. Because the schizophrenic and EPI-SZ patients had very similar clinical symptoms, it is unlikely that symptoms can explain the reduced N1s in the schizophrenic group. N1 amplitude has been reported to be affected by both arousal (Rockstroh et al 1994; Wagner et al 1996) and selective attention (Hansen and Hillyard 1983), both of which are often impaired in schizophrenia. Unfortunately, we have no indication whether the schizophrenic patients were significantly impaired in either arousal or selective attention.

Our data suggest that the auditory N1 is sensitive and relatively specific to pathophysiologic aspects of schizophrenia that are not involved in the pathogenesis of epilepsy-related psychosis. Although psychosis may emerge as a final common pathway of multiple neuropathologic processes associated with disruptions of P300 amplitude, our results reinforce the concept that schizophrenia may be associated with subtle and relatively specific neural insults. Given that the auditory N1 generators have been localized to frontotemporal circuits (Näätänen and Picton 1987), these are the most likely locations where the specific pathophysiology of schizophrenia will be revealed. Although this location is fairly broad, recent animal studies of the N1 have begun to suggest that N1 reductions specific to schizophrenia may be due to deficits in layer V of the primary auditory cortex or the *N*-methyl-D-aspartate (NMDA) neurotransmitter systems (Javitt et al 2000). It is unknown at present whether patients with epilepsy or EPI-SZ are free of deficits in this cortical layer

or in NMDA. Understanding the specificity of N1 reduction to schizophrenia and the mechanisms responsible for it awaits careful study of neurotransmitter systems and neural structures involved in generating N1 and the various clinical and cognitive correlates of N1 reduction, and perhaps a finer-grained analysis of the N1 subcomponents. It should be noted that we may not have had the power to detect N1 reductions in EPI-SZ patients due to the small sample, although a power analysis showed that six subjects would provide a power of .60 to detect the schizophrenic N1 effect.

Although we included epilepsy patients with various foci and syndromes, there were inadequate numbers in any subgroups to allow solid statistical comparisons between them. Indeed, attempts to link P300s recorded from specific scalp sites in patients with epilepsy with the locus of seizure focus (Puce and Bladin 1991) or even lateralized temporal lobe excision (Johnson 1988) have generally been unsuccessful, probably because of unknown contributions from multiple generators and the role of volume conduction. Similarly, although various subcomponents of N1 emanate from temporal and frontal lobe structures, neither of the epilepsy groups (in general having seizure foci in both temporal and frontal lobe structures) exhibited N1 amplitude reductions.

N1 and P300 latency delay in our epilepsy group patients is consistent with other studies (Drake et al 1986; Puce and Bladin 1991; Triantafyllou et al 1992; Verleger et al 1997). Like Verleger et al (1997), we found significant slowing of auditory but not visual P300 in the patients with epilepsy, but unlike them, we saw no evidence of P300 slowing associated with duration of epilepsy. The auditory P300 at Fz was not significantly slowed in the epilepsy patients, but was remarkably slowed in EPI-SZ patients, suggesting a delayed cortical response to the novelty features of the oddball stimuli. Slowing of the auditory N1 and P300 in epilepsy patients might be related to temporal lobe white matter volume reductions (Marsh et al 1997a, 1997b).

The origins of psychiatric illness in schizophrenic and EPI-SZ patients may be fundamentally different, yet may involve shared pathophysiology mechanisms as the psychotic processes develop. Schizophrenialike symptoms in other neuropathologic conditions may represent phenocopies of schizophrenia that, although having a separate etiology, share certain pathophysiological mechanisms that give rise to psychosis through a final common pathway. P300 amplitude appears to be sensitive to this pathway but, as such, is perhaps a poor candidate endophenotype for genetic studies of schizophrenia. In contrast, the N1 amplitude reduction that appears to be more specific to the core pathophysiology of schizophrenia deserves more study.

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References

- Blackwood D, Whalley L, Christie J, Blackburn I, St Clair D, McInnes A (1987): Changes in auditory P3 event-related potential in schizophrenia and depression. *Br J Psychiatry* 150:154–160.
- Bredkjaer SR, Mortensen PB, Parnas J (1998): Epilepsy and non-organic non-affective psychosis. National epidemiologic study. *Br J Psychiatry* 172:235–238.
- Coppola R (1979): Isolating low frequency activity in EEG spectrum analysis. *Electroencephalogr Clin Neurophysiol* 46:224–226.
- Donchin E (1981): Surprise! ... Surprise? *Psychophysiology* 18:493–513.
- Drake ME, Burgess RJ, Gelety TJ, Ford CE, Brown ME (1986): Long latency auditory event-related potentials in epilepsy. *Clin Electroencephalogr* 17:10–13.
- Endicott J, Spitzer RL (1978): A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 35:837–844.
- Ford J, Mathalon D, Marsh L, Faustman W, Harris D, Hoff A, et al (1999a): P300 amplitude is related to clinical state in severely and moderately ill schizophrenics. *Biol Psychiatry* 46:94–101.
- Ford JM (1999): Schizophrenia: The broken P300 and beyond. *Psychophysiology* 36:667–682.
- Ford JM, Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A (1996): Effects of cortical gray matter, attention, and schizophrenia on P300 amplitude. In: Ogura C, Koga Y, Shimokochi M, editors. *Recent Advances in Event-Related Brain Potential Research: Proceedings of the 11th International Conference on Event-Related Potentials (EPIC)*, Okinawa, Japan, June 25–30, 1995. Amsterdam: Elsevier, 916–921.
- Ford JM, Roth WT, Isaacks BG, Tinklenberg JR, Yesavage J, Pfefferbaum A (1997): Automatic and effortful processing in aging and dementia: Event-related brain potentials. *Neurobiol Aging* 18:169–180.
- Ford JM, Roth WT, Kopell BS (1976): Attention effects on auditory evoked potentials to infrequent events. *Biol Psychol* 4:65–77.
- Ford JM, Roth WT, Menon V, Pfefferbaum A (1999b): Failures of automatic and strategic processing in schizophrenia: Comparisons of event-related potential and startle blink modification. *Schizophr Res* 37:149–163.
- Ford JM, Sullivan EV, Marsh L, White PM, Lim KO, Pfefferbaum A (1994a): The relationship between P300 amplitude and regional gray matter volumes depends upon the attentional system engaged. *Electroencephalogr Clin Neurophysiol* 90:214–228.
- Ford JM, White PM, Csernansky J, Faustman WO, Roth WT, Pfefferbaum A (1994b): ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 36:153–171.
- Frangou S, Sharma T, Alarcon G, Sigmudsson T, Takei N, Binnie C, Murray RM (1997): The Maudsley family study. II. Endogenous event-related potentials in familial schizophrenia. *Schizophr Res* 23:45–53.
- Giard MH, Perrin F, Echallier JF, Thevenet M, Froment JC, Pernier J (1994): Dissociation of temporal and frontal components in the human auditory N1 wave: A scalp current density and dipole model analysis. *Electroencephalogr Clin Neurophysiol* 92:238–252.
- Gratton G, Coles MGH, Donchin E (1983): A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 55:468–484.
- Grunewald T, Beck H, Lehnertz K, Blumcke I, Pezer N, Kutas M, et al (1999): Limbic P300s in temporal lobe epilepsy with and without Ammon's horn sclerosis. *Eur J Neurosci* 11:1899–1906.
- 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.
- Halgren E, Squires N, Wilson C, Rohrbaugh J, Babb T, Crandall P (1980): Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 210:803–805.
- Hansen JC, Hillyard SA (1983): Selective attention to multidimensional auditory stimuli. *J Exp Psychol* 9:1–19.
- Hedlund JL, Vieweg BW (1980): The Brief Psychiatric Rating Scale (BPRS): A comprehensive review. *J Operational Psychiatry* 11:48–64.
- Javitt DC, Lindsley CE, Schroeder CE (2000): NMDA-mediated neurophysiologic deficits in schizophrenia. *Biol Psychiatry* 47:173S.
- Johnson R (1988): Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. *Brain* 111:1517–1529.
- Johnstone EC, Owens DGC, Frith CD, Crow TJ (1986): The relative stability of positive and negative features in chronic schizophrenia. *Br J Psychiatry* 150:141–151.
- Marsh L, Morrell MJ, Shear PK, Sullivan EV, Freeman H, Marie A, et al (1997a): Cortical and hippocampal volume deficits in temporal lobe epilepsy. *Epilepsia* 38:576–587.
- Marsh L, Sullivan E, Spears S, Sung T, Lim K, Morrell M, Pfefferbaum A (1997b): Clinical symptoms and MRI abnormalities in schizophrenia and epilepsy. *Schizophr Res* 24:151–152.
- Mathalon D, Ford J, Sullivan E, Lim K, Pfefferbaum A (1999): ERP and MRI reflections of the longitudinal course of schizophrenia. *Psychophysiology* 36:S13.
- 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 MJ, Pfefferbaum A (2000b): P300 reduction and prolongation with illness duration in schizophrenia. *Biol Psychiatry* 47:413–427.

- McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, Jolesz FA (1993): Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Arch Gen Psychiatry* 50:190–197.
- McKenna PJ, Kane JM, Parrish K (1985): Psychotic syndromes in epilepsy. *Am J Psychiatry* 142:895–904.
- Miller GA, Gratton G, Yee CM (1988): Generalized implementation of an eye movement correction procedure. *Psychophysiology* 25:241–243.
- Mueser KT, Douglas MS, Bellack AS, Morrison RL (1991): Assessment of enduring deficit and negative symptom subtypes in schizophrenia. *Schizophr Bull* 17:565–582.
- Näätänen R, Picton T (1987): The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology* 24:375–425.
- Nelson CA, Collins PF, Torres F (1991): P300 brain activity in seizure patients preceding temporal lobectomy. *Arch Neurol* 48:141–147.
- Oades R, Dittmann-Balcar A, Zerbin D (1997): Development and topography of auditory event-related potentials (ERPs): Mismatch and processing negativity in individuals 8–22 years of age. *Psychophysiology* 34:677–693.
- O'Donnell B, McCarley R, Potts G, Salisbury D, Nestor P, Hirayasu Y, et al (1999): Identification of neural circuits underlying P300 abnormalities in schizophrenia. *Psychophysiology* 36:388–398.
- Overall JE, Gorham DR (1962): The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799–812.
- Overall JE, Hollister L, Pichot R (1967): Major psychiatric disorders. A four-dimensional model. *Arch Gen Psychiatry* 16:146–151.
- 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* 46:1035–1046.
- Pfohl B, Winokur G (1982): The evolution of symptoms in institutionalized hebephrenic/catatonic schizophrenics. *Br J Psychiatry* 141:567–572.
- Pogue-Geile MF, Harrow M (1985): Negative symptoms in schizophrenia: Their longitudinal course and prognostic significance. *Schizophr Bull* 11:427–439.
- Polich J, Hoffman LD (1998): P300 and handedness: On the possible contribution of corpus callosal size to ERPs. *Psychophysiology* 35:497–507.
- Polich J, Ladish C, Bloom FE (1990): P300 assessment of early Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* 77:179–189.
- Porjesz B, Begleiter H (1993): Neurophysiological factors associated with alcoholism. In: Hunt WA, Nixon SJ, editors. *Alcohol-Induced Brain Damage. NIAAA Research Monograph #22*. Rockville, MD: Public Health Service, 89–120.
- Pritchard WS (1986): Cognitive event-related potential correlates of schizophrenia. *Psychol Bull* 100:43–66.
- Puce A, Bladin PF (1991): Scalp and limbic P3 event-related potentials in the assessment of patients with temporal lobe epilepsy. *Epilepsia* 32:629–634.
- Putnam KM, Harvey PD, Parrella M, White L, Kincaid M, Powchik P, Davidson M (1996): Symptom stability in geriatric chronic schizophrenic inpatients: A one-year follow-up study. *Biol Psychiatry* 39:92–99.
- Ramachandran G, Porjesz B, Begleiter H, Litke A (1996): A simple auditory oddball task in young adult males at high risk for alcoholism. *Alcohol Clin Exp Res* 20:9–15.
- Rao KM, Ananthnarayanan CV, Gangadhar BN, Janakiramaiah N (1995): Smaller auditory P300 amplitudes in schizophrenics in remission. *Neuropsychobiology* 32:171–174.
- Reite M, Adams M, Simon J, Teale P, Sheeder J, Richardson D, Grabbe R (1994): Auditory M100 component 1: Relationship to Heschl's gyri. *Brain Res Cogn Brain Res* 2:13–20.
- Reite M, Teale P, Zimmerman J, Davis K, Whalen J, Edrich J (1988): Source origin of a 50-msec latency auditory evoked field component in young schizophrenic men. *Biol Psychiatry* 24:495–506.
- Rockstroh B, Muller M, Wagner M, Cohen R, Elbert T (1994): Event-related and motor responses to probes in a forewarned reaction time task in schizophrenic patients. *Schizophr Res* 13:23–34.
- Roth WT, Ford JM, Lewis SJ, Kopell BS (1976): Effects of stimulus probability and task-relevance on event-related potentials. *Psychophysiology* 13:311–317.
- Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS (1981): Auditory event-related potentials in schizophrenia and depression. *Psychiatry Res* 4:199–212.
- Roth WT, Tecce JJ, Pfefferbaum A, Rosenbloom M, Callaway E (1984): ERPs and psychopathology: Behavior process issues. In: Karrer R, Cohen J, Tueting P, editors. *Brain and Information: Event-Related Potentials*. New York: New York Academy of Science, 496–522.
- Ruchkin DS, Glaser E (1978): Simple digital filters for examining CNV and P300 on a single-trial basis. In: Otto DA, editor. *Multidisciplinary Perspectives in Event-Related Potential Brain Research*. Washington, DC: U.S. Government Printing Office, 579–581.
- Salisbury DF, Shenton M, McCarley RW (1999): P300 topography differs in schizophrenia and manic psychosis. *Biol Psychiatry* 45:98–106.
- Scherg M, von Kramon D (1986): Evoked dipole sources of the human auditory cortex. *Electroencephalogr Clin Neurophysiol* 65:344–360.
- Shelley A, Silipo G, Javitt D (1999): Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: Implications for theories of cortical dysfunction. *Schizophr Res* 37:65–79.
- Slater E, Beard AW (1963): The schizophrenia-like psychoses of epilepsy i. Psychiatric aspects. *Br J Psychiatry* 109:95–150.
- Smith ME, Halgren E, Sokolik M, Baudena P, Musolino A, Liegeois-Chauvel C, Chauvel P (1990): The intracranial topography of the P3 event-related potential elicited during auditory oddball. *Electroencephalogr Clin Neurophysiol* 76:235–248.
- Smith ME, Stapleton JM, Halgren E (1986): Human medial temporal lobe potentials evoked in memory of language tasks. *Electroencephalogr Clin Neurophysiol* 63:145–159.
- Soysal A, Atakli D, Atay T, Altintas H, Baybas S, Arpacı B (1999): Auditory event-related potentials (P300) in partial and generalized epileptic patients. *Seizure* 8:107–110.
- Spitzer RL, Williams JBW, Gibbon M, First MB (1992): The

- structured clinical interview for DSM-III-R (SCID) 1. History, rationale, and description. *Arch Gen Psychiatry* 49:624–629.
- Steinhauer SR, Hill SY (1993): Auditory event-related potentials in children at high risk for alcoholism. *J Stud Alcohol* 54:408–421.
- Triantafyllou N, Zalonis I, Kokotis P, Anthracopoulos M, Siafakas A, Malliara S, et al (1992): Cognition in epilepsy: A multichannel event related potential (P300) study. *Acta Neurol Scand* 86:462–465.
- Turetsky B, Colbath EA, Gur RE (1998): P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. *Biol Psychiatry* 43:84–96.
- Verleger R, Lefebvre C, Wieschemeyer R, Kompf D (1997): Event-related potentials suggest slowing of brain processes in generalized epilepsy and alterations of visual processing in patients with partial seizures. *Cogn Brain Res* 5:205–219.
- Wagner M, Rendtorff N, Kathmann N, Engel RR (1996): CNV, PINV and probe-evoked potentials in schizophrenics. *Electroencephalogr Clin Neurophysiol* 98:130–143.
- Woods DL, Clayworth CC, Knight RT, Simpson GV, Naeser MA (1987): Generators of middle- and long-latency auditory evoked potentials: Implications from studies of patients with bitemporal lesions. *Electroencephalogr Clin Neurophysiol* 68:132–148.
- Yanai I, Fujikawa T, Osada M, Yamawaki S, Touhouda Y (1997): Changes in auditory P300 in patients with major depression and silent cerebral infarction. *J Affect Disord* 46:263–271.