
P300 Reduction and Prolongation with Illness Duration in Schizophrenia

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Background: *The P300 component of the auditory event-related potential (ERP) is both reduced in amplitude and delayed in schizophrenia. P300 is prolonged and, less consistently, reduced with normal aging. Additional latency delays are observed in neurodegenerative disorders. We asked whether P300 is reduced and delayed with longer illness duration in schizophrenia, consistent with a neurodegenerative process.*

Methods: *P300 amplitude and latency were recorded to infrequent auditory target stimuli from 35 men with schizophrenia (DSM-III-R) and 26 control men. Effects of current age, age of onset, and duration of illness on P300 were assessed using regression analysis.*

Results: *P300 amplitude showed no age-related decrease in either group; however, among schizophrenic participants, P300 amplitude correlated positively with onset age and negatively with illness duration. P300 latency correlated positively with age in schizophrenic participants and also tended to increase with age in controls. Slopes of the latency–age relationships were significantly greater in schizophrenic participants than in control participants. Latency also correlated positively with illness duration but showed no relationship to onset age.*

Conclusions: *P300 amplitude and latency are reduced and delayed with longer illness duration in schizophrenia, consistent with a progressive pathophysiological process. Reduced P300 amplitude may also be a marker of an early onset variant of schizophrenia.* Biol Psychiatry 2000;47:413–427 © 2000 Society of Biological Psychiatry

Key Words: P300, schizophrenia, onset, duration, age, neurodegeneration

Introduction

Schizophrenia is a lifetime neuropsychiatric illness encompassing subtle prodromal symptoms during childhood, onset of psychotic symptoms in early adulthood, a variable course, and a heterogeneous long-term outcome (Angst 1988; McGlashan 1988). Current etiological views of schizophrenia emphasize a neurodevelopmental insult (Murray 1994; Weinberger and Lipska 1995), in part because structural (e.g., Degreef et al 1992; Lim et al 1996b; Nopoulos et al 1995) and functional (e.g., Andreasen et al 1992; Gur et al 1995; Salisbury et al 1998) brain abnormalities, as well as cognitive deficits (e.g., Bilder et al 1992; Censits et al 1997; Hoff et al 1992) have been observed in patients at the time of their first psychotic episode. Whether the pathophysiology of schizophrenia also includes progressive or neurodegenerative processes operating over the course of the illness (at least in the subgroup of patients with poor clinical, cognitive, and social outcomes) remains controversial (Woods 1998).

Clinically, the course of illness in schizophrenia ranges from episodic to chronic unremitting, with long-term outcomes ranging from clinical improvement to a severely deteriorated residual state (e.g., Ciompi 1980; Huber et al 1980; McGlashan 1988; for reviews, see Angst 1988). Despite this heterogeneity in the illness course, there is evidence of general diminution or amelioration of positive psychotic symptoms and persistence or increased prominence of negative symptoms late in the illness course (e.g., Ciompi 1980; Davidson et al 1995; Huber et al 1980; Shultz et al 1997; for review, see McGlashan and Fenton 1992). These findings suggest the operation of a progressive pathophysiological process, perhaps interacting with normal aging processes. In addition, although multiple studies have documented cognitive deficits in schizophrenia that appear to be relatively stable or to improve over time (for review, see Rund 1998), other studies of chronic patients have found evidence of modest cognitive decline with increasing age, either cross-sectionally (Davidson et al 1996; Davidson et al 1995; Harvey et al 1995) or longitudinally (Harvey et al 1999). Moreover, a considerable proportion of institutionalized geriatric patients with schizophrenia have a poor outcome

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including severe dementia (e.g., Angst 1988; Ciompi 1980; Davidson et al 1996; Davidson et al 1995; Harvey et al 1995; Purohit et al 1993), yet lack the neurohistological pathology at autopsy characteristic of Alzheimer's or other neurodegenerative diseases (e.g., Arnold et al 1998; Haroutunian et al 1994; Murphy et al 1998; Purohit et al 1993). Thus, among the heterogeneous illness courses observed in schizophrenia, there are suggestions from both clinical and neurocognitive data that the pathophysiology of schizophrenia involves progression, at least in a subset of patients, but more direct measures of brain integrity and function are necessary to address this question definitively.

Postmortem neuropathological studies provide one source of data regarding the neurodegenerative hypothesis and for the most part have failed to find evidence of gliosis in schizophrenia (e.g., Arnold et al 1998; Bruton et al 1990; Roberts et al 1986). It has been noted, however, (Garver 1997; Woods 1998) that brain-tissue loss can also occur by apoptosis, or programmed cell death, which does not cause inflammation and associated gliosis (Margolis et al 1994). In addition, because postmortem studies can only reveal the end products of progressive neuropathological processes, *in vivo* markers of neurodegeneration are needed to study the progressive pathophysiology of schizophrenia over the illness course.

A primary source of *in vivo* data is quantitative volumetric brain imaging using computed tomography (CT) or magnetic resonance (MRI), which to date has been equivocal regarding the question of progressive brain volume deficits in schizophrenia. Structural brain imaging provides relatively static measures of brain integrity that may require large sample sizes cross-sectionally and relatively long time intervals longitudinally to detect evidence of progressive brain volume changes. Cross-sectional studies generally have not found significant correlations between brain structure size and duration of illness (e.g., Lauriello et al 1997; Lim et al 1996a; Marsh et al 1994; Pfefferbaum et al 1988; Weinberger et al 1979; Zipursky et al 1992), with some exceptions (e.g., DeLisi et al 1991a; O'Callaghan et al 1992; Woods and Wolf 1983). Early longitudinal studies often failed to show progressive brain volume decline (Degreef et al 1991; DeLisi et al 1991b; Hoffman et al 1991; Illowsky et al 1988; Sponheim et al 1991; Vita et al 1988), but more recent studies using larger samples and more sophisticated imaging methods are accumulating evidence supporting progression in schizophrenia (DeLisi et al 1997; DeLisi et al 1995; Gur et al 1998; Mathalon et al, *in press*), at least in a subgroup of patients (Davis et al 1998; Jacobsen et al 1998; Nair et al 1997; Rapoport et al 1997). Although these more recent data are suggestive of accelerated brain volume decline in schizophrenia, they do not provide direct evidence of

deterioration in neural function. Furthermore, volume changes resulting from non-neurological processes (e.g., changes in hydration, nutrition, or endocrine function) cannot be ruled out. Accordingly, corroborating data must be sought from *in vivo* markers of brain function, such as psychophysiological measures of brain activity extracted from the electroencephalogram (EEG).

Scalp-recorded event-related brain potentials (ERP) are intrinsically dynamic, have the potential to track functional brain changes over short time periods, and thus may provide biological markers of progressive neurophysiological deterioration in schizophrenia. One candidate marker of progression in schizophrenia is the P300 component of the ERP, a positive voltage deflection occurring approximately 300 msec following the presentation of an infrequent or unexpected target stimulus, usually measured in an auditory "oddball" paradigm (Donchin and Coles 1988). P300 amplitude reduction is a widely replicated finding in schizophrenia (for reviews, see Ford et al 1992; McCarley et al 1991; Pritchard 1986). Less consistently, P300 latency prolongation has also been reported in schizophrenia (e.g., Blackwood et al 1991; Coburn et al 1998; Eikmeier et al 1992; Pfefferbaum et al 1984b; Roth et al 1979; Roxborough et al 1993; St Clair et al 1989; Weir et al 1998).

P300 amplitude reflects task-related cognitive processes, such as attention, expectancies, and context updating (Donchin and Coles 1988; Johnson 1986; Verleger 1988). It also reflects the integrity of some structural characteristics of the brain, such as the volume of cortical gray matter (Ford et al 1994a; McCarley et al 1993). Reduction of P300 amplitude with normal aging has been shown in many studies (e.g., Ford and Pfefferbaum 1991; Goodin et al 1978a; Iragui et al 1993; Picton et al 1984; Polich 1991), with some exceptions (e.g., Patterson et al 1988; Pfefferbaum et al 1984a). Similarly, dementia has been associated with P300 amplitude reduction in several studies (Ford et al 1996b; Goodin et al 1978b; Pfefferbaum et al 1984b), but not all studies (Patterson et al 1988). P300 amplitude reduction in schizophrenia has been related to brain volume deficits (McCarley et al 1993), clinical symptoms (e.g., Egan et al 1994; Eikmeier et al 1992; Ford et al 1999; Mathalon et al 2000; McCarley et al 1991; Pfefferbaum et al 1989; Turetsky et al 1998a), and momentary or enduring attentional deficits (Ford et al 1994a; Fukuda et al 1997; Grillon et al 1990). Because it can potentially bridge the gap between the observations of brain volume decline and deterioration in clinical and cognitive function, P300 amplitude is a promising candidate marker of progressive neuropathological processes in schizophrenia. Consistent with this possibility, several studies of schizophrenic patients have shown P300 amplitude to be inversely correlated with age (Muir et al 1991),

illness duration (Olichney et al 1998), and percent time hospitalized since illness onset (O'Donnell et al 1995).

Substantial evidence exists that P300 amplitude reduction reflects not only the trait of schizophrenia, but can also fluctuate with clinical state. Evidence suggesting that P300 amplitude reduction is a trait marker of schizophrenia, possibly reflecting the underlying genetic vulnerability to the disease, includes findings of reduced P300 amplitude a) in patients whose symptoms have improved or largely remitted with medication (Blackwood et al 1987; Coburn et al 1998; Mathalon et al 2000; Pass et al 1980; Rao et al 1995; St Clair et al 1989; Turetsky et al 1998b); b) in first-episode patients (Hirayasu et al 1998; Salisbury et al 1998); and c) in unaffected first-degree relatives (e.g., Blackwood et al 1991; Frangou et al 1997; Kidogami et al 1992; Roxborough et al 1993; but for negative findings, see Friedman et al 1988). Moreover, some longitudinal reports indicate that P300 amplitude is stable over time and unrelated to changes in clinical status (Blackwood et al 1987; Ford et al 1994c; Juckel et al 1996; Turetsky et al 1998b); however, other studies also implicate P300 amplitude as a clinical-state marker in schizophrenia, including cross-sectional studies showing associations with clinical symptoms (e.g., Egan et al 1994; Eikmeier et al 1992; Ford et al 1999; Maeda et al 1996; Mathalon et al 2000; Pfefferbaum et al 1989; Roth et al 1980; Turetsky et al 1998a) as well as longitudinal studies showing sensitivity to clinical-state fluctuations over time (Asato et al 1996; Maeda et al 1996; Mathalon et al 2000; Turetsky et al 1998b) and to medication effects independent of clinical state (Coburn et al 1998; Hirayasu and Ogura 1996; Levit et al 1973; Umbricht et al 1998). These data underscore the conceptual point that a biological marker can reflect both trait and state aspects of schizophrenia. Thus, as a marker of both state and trait, P300 amplitude is particularly suitable for tracking progressive neuropathological processes over the long-term illness course.

P300 latency has been thought to reflect cognitive processing speed or efficiency (e.g., Kutas et al 1977) and has been shown to be increasingly delayed with normal aging (for review, see Polich 1996). To the extent that the course of schizophrenia follows a neurodegenerative path, it might be expected that P300 latency would show the kind of latency prolongation, relative to age-matched controls, that has been observed in elderly subjects with dementing diseases (for reviews, see Goodin 1990; Pfefferbaum et al 1990). Indeed, there have been reports of P300 latency prolongation in schizophrenic patients with longer illness durations (Frangou et al 1997; O'Donnell et al 1995; Olichney et al 1998).

The sensitivity of P300 latency, and to a lesser extent amplitude, to normal aging and dementia supports their

potential to serve as biological markers of progressive brain changes. Arguably, any inference of neurodegeneration or progression in schizophrenia based on P300 amplitude reduction or latency prolongation would need to demonstrate age-related changes in excess of that resulting from normal aging. Recent studies (Frangou et al 1997; O'Donnell et al 1995) have found that the relationship between age and P300 latency, but not amplitude, had a steeper slope in schizophrenic patients than in normal controls, consistent with a neurodegenerative process in schizophrenia. In the present study, we attempted to replicate these age–P300 latency effects in a sample of chronic schizophrenic patients and age-matched normal controls, with additional clarification of the age–P300 relationships in schizophrenia through consideration of the effects of age at illness onset and illness duration (which together sum to current age). Based on previous findings in the literature, we hypothesized that P300 amplitude and latency are markers of progressive brain changes in schizophrenia, with specific predictions that P300 will be smaller and later with longer illness duration and will show accelerated age relationships compared to normal controls. We also predicted that an earlier age at illness onset would be associated with a smaller P300 amplitude, but not a longer latency (Olichney et al 1998).

Methods and Materials

Participants

Demographic, clinical, and ERP descriptions of the subjects are summarized in Table 1.

PATIENTS. Male inpatients ($n = 35$) at the Palo Alto Department of Veterans Affairs Medical Center with DSM-III-R schizophrenia who did not have a current (<3 months) diagnosis of alcohol or drug dependence, a serious medical illness, or a hearing deficit greater than 30 dB in the better ear at 500, 1000, or 2000 Hz were recruited for study. ERP data from many of these patients have been included in prior reports (Ford et al 1994a, 1994b, 1994c, 1996a, 1999; Mathalon et al 2000). Fourteen of the patients had a past history of alcoholism by Research Diagnostic Criteria (Spitzer et al 1975), but none met these criteria in the 3 months prior to testing. Seven patients were medicated with typical antipsychotics at the time of testing, 26 had been drug-free for more than 14 days, and 2 patients had been drug free for fewer than 14 days.

Diagnosis and age at onset of schizophrenia were determined by consensus of the attending psychiatrist or psychologist performing a clinical interview and a trained interviewer using the SCID (Spitzer et al 1989). The symptoms of schizophrenia must have been present for 6 months, including an active phase of at least 1 week. Disease duration was defined as current age at testing minus estimated age at illness onset. Age at onset estimates were not available for 4 of the 35 subjects. Clinical symptom severity at the time of testing was assessed in a

Table 1. Means and Standard Deviations (SD) for N100, P300, and Clinical Variables

Variable	Schizophrenic subjects					
	Normal control subjects (<i>n</i> = 26)		Total sample (<i>n</i> = 35)		Comorbids excluded (<i>n</i> = 21)	
	Mean	SD	Mean	SD	Mean	SD
N100 (Cz)						
Amplitude (μ V)	-8.21	2.6	-5.43	3.1	-5.60	3.3
Latency (msec)	107	12.6	108	16.7	107	16.7
P300 (Fz)						
Amplitude (μ V)	6.47	4.4	5.32	3.2	5.67	3.6
Latency (msec)	338	41.2	369	57.1	367	56.6
P300 (Cz)						
Amplitude (μ V)	7.73	4.8	6.63	3.3	7.29	3.6
Latency (msec)	363	80.1	356	53.3	359	65
P300 (Pz)						
Amplitude (μ V)	8.76	4.2	6.81	3.1	6.91	3.3
Latency (msec)	351	42.2	366	56.3	366	55.3
Age (years)	38.8	9.0	38.6	7.3	39.2	8.4
Onset age (years)			25.0	8.0	26.4	8.7
Illness duration (years)			13.6	7.2	13.5	7.2
Total BPRS			48.2	7.2	47.8	8.5

semi-structured interview by two trained raters using the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1988).

CONTROLS. Healthy control men (*n* = 26) recruited by newspaper advertisement and word-of-mouth were interviewed by a psychiatrist, psychologist, or trained research assistant using the Schedule for Affective Disorders and Schizophrenia (Spitzer et al 1975). Exclusion criteria included DSM-III-R diagnosis for major psychiatric disorders, current alcohol or drug abuse, and past alcohol or drug dependence. All subjects were also interviewed with a semi-structured questionnaire to quantify parameters of alcohol intake. Subjects who drank more than 50 g/day of alcohol for 1 month were excluded. Subjects were also excluded if they had a history of other significant medical or neurological illness, a history of head injury resulting in loss of consciousness greater than 30 min, and hearing deficits greater than 30 dB at 500, 1000, and 2000 Hz in their better ear.

ERP Recording and Analysis

ERPs were collected during an auditory "oddball" target detection task in which frequent tones (500 Hz, 80 dB SPL, 50 msec duration) occurred on 80% of the trials, and target tones (1000 Hz, 80 dB SPL, 50 milliseconds duration) occurred on 20% of the trials. The interstimulus interval was 1.5 sec. Subjects pressed a button to rare events with their preferred hand, giving equal emphasis to speed and accuracy. Subjects participated in the protocol on 2 consecutive days as part of a study of ERP component reliability.

We report EEG recorded from the frontal (Fz), central (Cz), and parietal (Pz) midline sites, referenced to a sternovertebral electrode with a balancing circuit to minimize EKG artifacts (Ford and Pfefferbaum 1991). EEG data were recorded with a bandpass of .05–30 Hz. Vertical EOG was recorded from

electrodes placed above and below the right eye and horizontal EOG from electrodes placed at the outer canthus of each eye.

DATA SCREENING. Single trials were individually screened by computer algorithm before being included in the averages. First, trials on which EEG at any electrode site saturated the A/D converter ($> \pm 250\mu$ V) were rejected. Next, single trials at each electrode were individually corrected for the effects of eye blinks and eye movements (Miller et al 1988). Trials with button presses occurring before 100 msec or after 1150 msec were excluded, as were those with incorrect button presses. Each averaged ERP waveform comprised 30 or more trials.

PEAK IDENTIFICATION. Before peak identification, EEG was filtered with a .5 Hz (down 3 dB) high pass filter and a 12.4 Hz (down 3 dB) low pass filter (Ford and Pfefferbaum 1991). For the analyses presented here, P300 was measured as the most positive peak at Fz, Cz, and Pz between 280 and 600 msec, and N100 was measured as the most negative peak between 50 and 150 msec at Cz.

ERP peak and latency values from day 1 and day 2 of this study were averaged together in this analysis to improve the cross-time reliability of the estimates.

Statistical Analysis

Group and topographic differences in P300 amplitude and latency were assessed using repeated measures analysis of variance (ANOVA), with follow-up *t* tests to parse interaction effects. Age effects on P300 amplitude and latency were assessed using multiple regression models where P300 was predicted from Age, Group (schizophrenic participants vs. control participants), and the Age \times Group interaction. Group differences in the slopes of the P300–age regression lines were tested by assessing the increment in prediction afforded by the interaction term in the

regression model. For schizophrenic participants alone, P300 amplitude and latency were each correlated with age at onset and disease duration, the two time epochs that together sum to a person's current age. The contributions of clinical symptoms, medication status, and past history of alcohol abuse or dependence were also assessed. Parallel analyses of N100 values were performed. One-tailed significance tests ($\alpha = .05$) were used to test our a priori hypotheses concerning P300 amplitude reduction and latency prolongation in normal aging and in schizophrenic participants relative to control participants, with additional predictions of greater reduction and prolongation for patients with longer illness durations and greater reductions for patients with earlier illness onset. Two-tailed tests were used to assess the relationship between P300 latency and illness onset, as no relationship was expected. Two subjects had technically unusable ERP data from single electrode leads, one from Fz and the other from Cz, and were thus excluded from analyses involving these leads.

Results

P300 Amplitude

COMPARISON BETWEEN SCHIZOPHRENIC AND CONTROL PARTICIPANTS. The ANOVA Group effect was not significant but showed a trend in the predicted direction of reduced P300 amplitude in schizophrenia [$F(1,57) = 1.9, p < .09$, one-tailed]. There was a significant Site effect [$F(1,57) = 31.43, p \leq .0001$], indicating a parietally maximal P300, but no Group \times Site interaction [$F(2,114) = 1.85, p = .16$]. Individual t tests at each site detected a difference in group means (see Table 1) only at Pz [$t(59) = -2.08, p = .02$, one-tailed]. The Group effect can be seen in Figure 1.

RELATIONSHIP WITH AGE IN SCHIZOPHRENIC PARTICIPANTS AND CONTROL PARTICIPANTS. Age-related change in P300 amplitude was assessed separately in both schizophrenic and control participants. The correlations between P300 amplitude and age were not significant in either group (see Table 2). In multiple regression analyses predicting P300 amplitude at each electrode site from Age, Group, and the Age \times Group interaction, the interaction term failed to provide a significant increment in prediction in each case (Fz: R^2 change = 0, $p = .93$; Cz: R^2 change = .016, $p = .35$; Pz: R^2 change = .025, $p = .21$), indicating that the slopes of the age-regression lines (Figure 2, upper) were not significantly different in the schizophrenic participants and control participants at any lead.

RELATIONSHIP WITH ONSET AGE AND ILLNESS DURATION IN SCHIZOPHRENIC PARTICIPANTS. P300 amplitudes at all three leads were significantly correlated with both age at illness onset and illness duration (Table 2)

but in opposite directions. Positive correlations with age at onset indicated that smaller P300 amplitudes were observed in patients who became ill earlier, whereas negative correlations with illness duration indicated smaller amplitudes in those patients who had been ill longer (Figure 3, upper). A significant inverse correlation was observed between onset age and illness duration, yet both were positively correlated with age (Table 2). This indicated that in the present sample, older patients tended to have later illness onset and longer illness duration, even though patients who had been ill longer generally tended to have earlier illness onset.

P300 Latency

COMPARISON BETWEEN SCHIZOPHRENIC AND CONTROL PARTICIPANTS. The repeated measures ANOVA did not detect significant effects for Group [$F(1,57) = 1.09, p = .30$] or Site [$F(2,114) = .389, p = .68$] for P300 latency; however, there was a significant Group \times Site interaction [$F(2,114) = 3.52, p = .03$]. Follow-up one-tailed t tests indicated that P300 latency was later in schizophrenic participants than in control participants (see Table 1) at Fz [$t(58) = 2.28, p = .013$], but not at Cz ($p = .33$) or Pz ($p = .12$).

RELATIONSHIP WITH AGE IN SCHIZOPHRENIC AND CONTROL PARTICIPANTS. One-tailed correlations between P300 latency and age (Table 2) were positive and significant in the schizophrenic participants across all three leads, but there was only a positive trend ($p = .06$) at Pz in the controls. Multiple regression analyses were performed predicting P300 latency from Age, Group, and the Group \times Age interaction at each site to test for significant group differences in the slopes of the P300 latency–age relationships. The slopes were significantly different at Fz (R^2 change = .115, $p = .006$) and Cz (R^2 change = .116, $p = .008$), with a trend at Pz (R^2 change = .041, $p = .08$), indicating that P300 latency increased with age at a faster rate in the schizophrenics than in the controls (Figure 2, lower).

RELATIONSHIP WITH ONSET AGE AND ILLNESS DURATION IN SCHIZOPHRENIC PARTICIPANTS. P300 latency was not significantly correlated with age at illness onset but showed significant positive correlations with illness duration at all three sites (Table 2), indicating that patients with longer illness durations had slower P300 latencies (see Figure 3, lower).

Medication Status, Symptom Severity, and History of Comorbidity for Alcoholism

The majority (26 out of 35) of the schizophrenic participants in this study were tested while undergoing drug

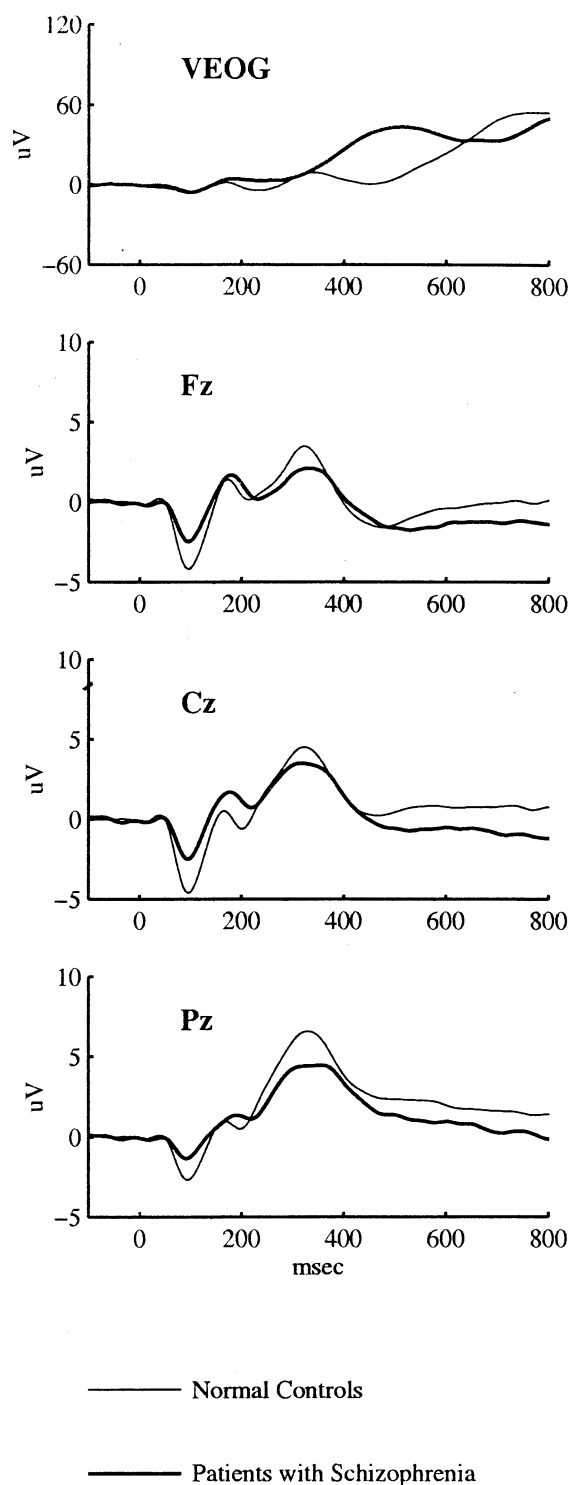


Figure 1. Grand averages of ERPs elicited by target tones from normal controls ($n = 26$) and patients with schizophrenia ($n = 35$). Waveforms are shown for VEOG, Fz, Cz, and Pz. VEOG activity was removed from the ERPs mathematically but is shown here for illustrative purposes. Positive voltages at the scalp are plotted up. X-axis reflects time in milliseconds, and Y-axis reflects amplitude in microvolts.

washout for a clinical trial (Ford et al 1994c). The remaining patients were on typical neuroleptics when tested. There were no significant differences (by 2-tailed t test) on any ERP, clinical, or demographic variable between the medicated and unmedicated patient groups. In addition, clinical severity as assessed by total BPRS scores was not associated with any demographic or ERP variable.

Alcoholism has been associated with increases in P300 latency and reduction of its amplitude (Pfefferbaum et al 1991; Porjesz and Begleiter 1993). Because our sample included patients ($n = 14$) who had a past history, but not a current history, of alcohol dependence (comorbid), we evaluated whether this history could account for any of the observed relationships of age, onset age, or illness duration with P300 amplitude and latency. First, we recalculated the correlations within the subgroup of patients who had no prior history of alcohol dependence ($n = 21$). Essentially, the same pattern of relationships emerged for both P300 latency and amplitude (see Table 2): P300 latency remained positively correlated with age and illness duration but not onset age, whereas P300 amplitude remained uncorrelated with age, but was positively correlated with onset age and negatively correlated with illness duration. In further multiple regression analyses, the slopes of the linear relationships of P300 amplitude and latency with age, age at onset, and illness duration were each compared between the schizophrenic participants with and without comorbid alcohol dependence histories. In no case were the slopes significantly different in these two patient subgroups. Thus, there was no evidence that past alcohol history among a subgroup of the patients included in the present analyses accounted for any of the observed relationships between P300, age, age at onset, or illness duration.

Exclusion of a statistical outlier, a 55-year-old patient with recent illness onset (falling >15 years beyond the rest of the sample), did not significantly change the pattern of significant correlations for P300 amplitude or latency. Thus, this patient was retained in the analyses.

N100

N100 values were analyzed only at Cz where amplitude was maximal. N100 was smaller in schizophrenic participants than in control participants [$t(59) = 3.6, p < .001$], but its peak latency was not slower. Neither N100 amplitude nor latency was associated with age among the schizophrenic participants or the control participants. Among the schizophrenic participants, neither N100 amplitude nor age was associated with age at onset or duration of illness.

Table 2. Pearson Correlations of P300 Amplitude and Latency with Age, Age of Onset, and Illness Duration

Variable	P300 amplitude			P300 latency			Clinical course	
	Fz	Cz	Pz	Fz	Cz	Pz	Onset age	Illness duration
Normal control subjects (<i>n</i> = 26)								
Age	.04	-.09	-.22	-.26	-.18	.32 ^a		
Schizophrenic subjects (<i>n</i> = 35)								
Age	.07	.17	.11	.42 ^c	.56 ^e	.53 ^d	.54 ^c	.40 ^b
Onset age	.49 ^c	.52 ^c	.58 ^d	-.07	.12	-.09		-.56 ^d
Illness duration	-.49 ^c	-.41 ^b	-.52 ^c	.48 ^c	.42 ^c	.64 ^e		
Schizophrenic subjects (<i>n</i> = 21) (excluding comorbid)								
Age	.06	.17	.21	.53 ^c	.53 ^c	.54 ^c	.63 ^c	.38
Onset age	.43 ^b	.42 ^b	.60 ^c	.09	.16	.04		-.48 ^b
Illness duration	-.54 ^c	-.43 ^b	-.55 ^c	.48 ^b	.44 ^b	.56 ^c		

^a*p* = .07^b*p* ≤ .05^c*p* ≤ .01^d*p* ≤ .001^e*p* ≤ .0001*p*-values for correlations are one tailed, except among age, onset age, and illness duration, as well as between onset age and P300 latency, which are two tailed.

Discussion

The major findings of this study are that P300 amplitude and latency are smaller and later in schizophrenic patients who have had a longer duration of illness, consistent with the hypothesis that the course of schizophrenia involves progressive decline in brain function. In addition, P300 amplitude, but not latency, is smaller in those patients with an earlier age at illness onset. These ERP measures reflect distinct neurocognitive functions, with P300 amplitude indexing attentional resources and latency indexing the speed with which these resources can be deployed. It appears that both of these functions, and by implication the brain substrates that subservise them, are compromised to a greater extent in the later stages of schizophrenia, with the additional suggestion that more prominent deficits in attentional resources may characterize schizophrenic patients with an earlier age at onset. Thus, although our illness-duration results support the potential roles of both P300 amplitude and latency as markers of progression in schizophrenia, it is likely that they index different pathophysiological processes, given their differential pattern of relationships with age at illness onset. Because P300 latency is known to increase with normal aging (for reviews, see Ford and Pfefferbaum 1985; Polich 1996) it was important to rule out the possibility that its prolongation with longer disease duration was simply a normal aging effect. Indeed, P300 latency increased over the young- to middle-adult age range faster in the schizophrenic patients than in the healthy control individuals, consistent with prior studies (Frangou et al 1997; O'Donnell et al 1995). As in the O'Donnell report (O'Donnell et al 1995), we found a stronger slope difference between schizophrenic participants and control par-

ticipants for frontal and central P300s than for the parietal P300. The relatively small correlation of P300 latency with age in the normal controls is probably due to the limited age range represented in our sample (age < 55), as studies with larger samples have noted a curvilinear relationship between P300 latency and age, with acceleration beginning between the ages of 45 and 60 years (e.g., Anderer et al 1996; Iragui et al 1993). The fact that P300 latency was associated with disease duration but not onset age suggests that the process responsible for the slowing of P300 probably begins at illness onset and continues over the illness course.

The finding that P300 amplitude was smaller in schizophrenic patients who had been ill longer is consistent with a deteriorating process operating over the course of the illness. Unlike P300 latency, P300 amplitude was also related to age at illness onset: The earlier the onset, the smaller the P300. The same pattern of results with respect to onset age and illness duration for P300 amplitude was recently reported (Olichney et al 1998) in a sample of older schizophrenic patients encompassing early- and late-onset ages. The association between onset age and P300 amplitude is consistent with studies reporting early-onset schizophrenia to exhibit greater severity of illness (e.g., Johnstone et al 1989; World-Health-Organization 1979), neuropsychological deficits (e.g., Heaton et al 1994; Hoff et al 1996; Jeste et al 1998; Johnstone et al 1989), and structural brain abnormalities (Aso et al 1995; DeLisi et al 1991a; Jeste et al 1998; but see Lim et al 1996a; Marsh et al 1997). Together these observations suggest that early-onset schizophrenia is a more severe variant of the disease for which P300 amplitude reduction may be a marker. Indeed, Olichney and colleagues

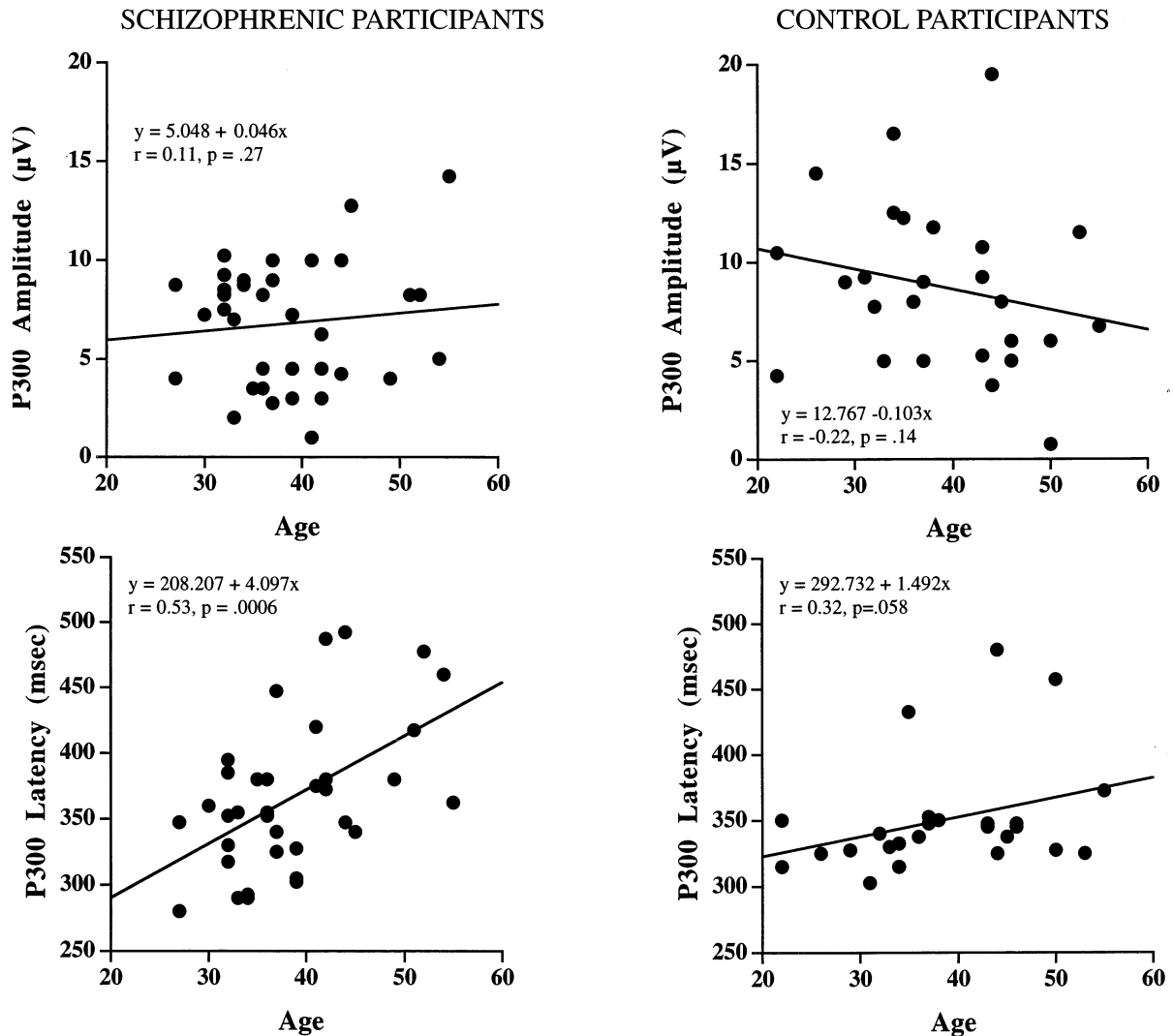


Figure 2. Upper: Relationships between P300 amplitude at Pz (μV) and age (years), for patients with schizophrenia (left) and age-matched controls (right). Lower: Same as above but for P300 latency at Pz (msec). Regression equations, Pearson correlation coefficients, and one-tailed significance levels are shown.

(Olichney et al 1998) reached this conclusion in their study of middle-aged and elderly schizophrenic patients, despite the fact that P300 amplitude reduction showed equivalent associations with both earlier onset age and longer disease duration. Because of the restricted age range of their sample, a relatively high correlation between age at onset and illness duration would be expected, making it difficult to disentangle their effects on P300. In the present study, in which the age range of the patient sample was relatively broad, onset age and illness duration shared only 31% of their variance ($r = -.56$) and therefore had potentially dissociable effects on P300 amplitude. This was confirmed by significant one-tailed semi-partial correlations of P300 amplitude (at Pz) with onset age partialling out illness duration (semi-partial $r =$

.34, $p = .014$) and with illness duration partialling out onset age (semi-partial $r = -.24$, $p = .055$). Controlling for their shared variance reduced both of the correlations, more so for illness duration than onset age, but showed that both of these aspects of the course of schizophrenic illness retained significant independent effects on P300 amplitude.

The attempt to disentangle the effects of age at onset, illness duration, and current age is fraught with difficulty because of the inherent dependency among these measures (current age = onset age + illness duration). Although there is no necessary relationship between any two of these variables, if the third is held constant (for example, by studying only older patients), the other two will be inversely correlated. If all three of these variables are

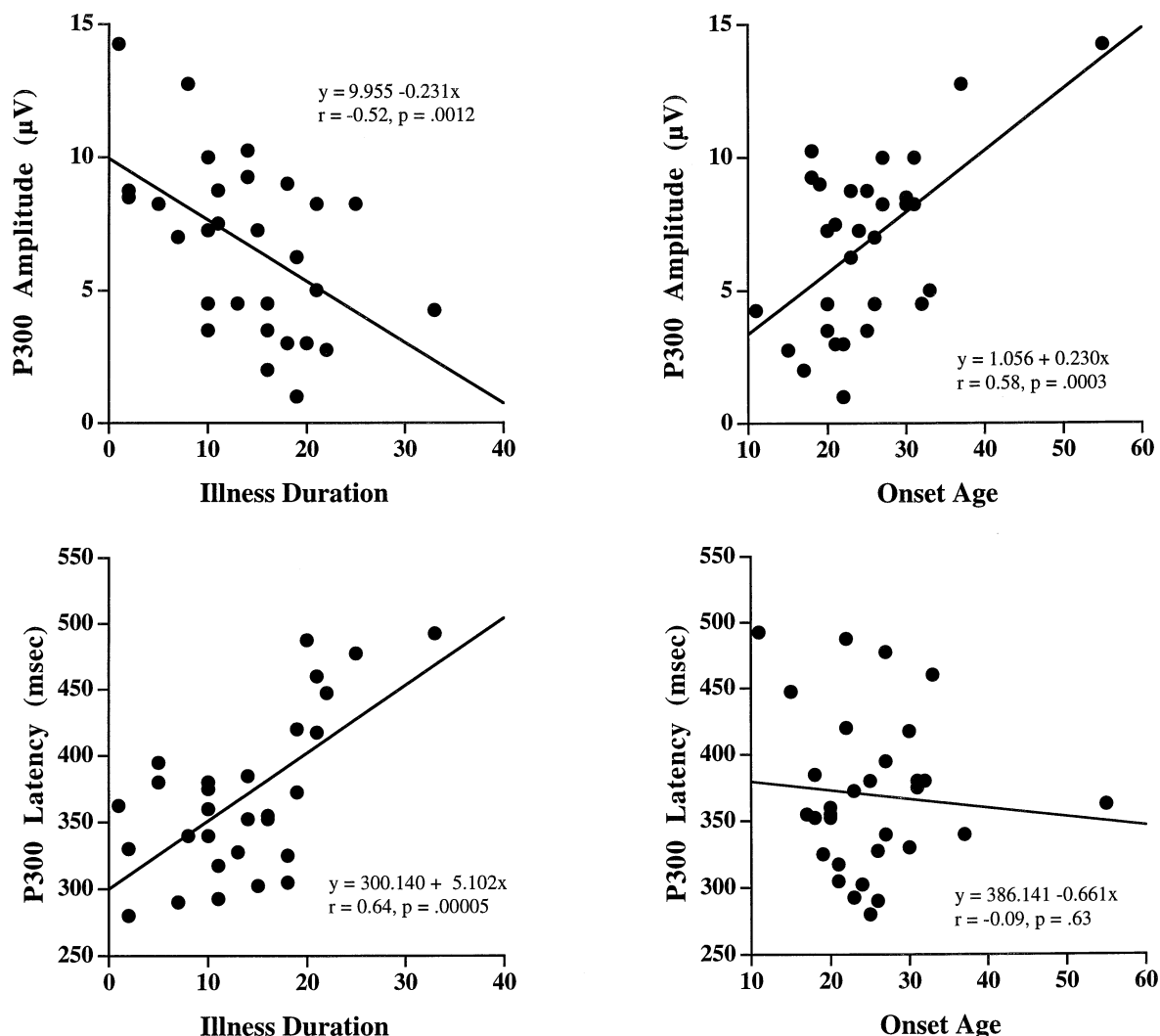


Figure 3. Upper: Relationships between P300 amplitude at Pz (μV) and (left) illness duration (years) and (right) age at onset of illness (years) for patients with schizophrenia. Lower: Same as above but for P300 latency at Pz (msec). Regression equations, Pearson correlation coefficients, and two-tailed significance levels are shown.

allowed to vary in the patient sample, the correlations observed among them will depend entirely on the particular demographic characteristics of the sample. Different questions may require different sampling strategies, and the results must be interpreted with the particular sample characteristics in mind. Thus, in the present sample of schizophrenic participants, current age was positively correlated with both duration of illness and onset age. P300 amplitude, unlike latency, did not show the expected correlation with current age in the schizophrenic participants, despite its reduction with longer illness duration. This lack of age correlation can be understood as resulting from the fact that the older patients tended to have later illness onsets (and hence, larger amplitudes) and longer illness durations (and hence, smaller amplitudes). The countervailing effects of onset age and illness duration on

P300 amplitude essentially eliminated the age relationship. This was not the case for P300 latency, where age at onset exerted no significant effect.

Intracranial recordings have suggested that the generators of the P300a wave, reflecting orientation of attention, include the inferior parietal, cingulate, and dorsolateral prefrontal cortex. The generators of the P300b wave, reflecting further encoding and processing of infrequent target stimuli, include the hippocampus, superior temporal sulcus, lateral orbitofrontal cortex, and intraparietal sulcus (Halgren et al 1998). In addition, recent fMRI studies of brain activation to infrequent target stimuli also suggest activation of the temporo-parietal cortex, anterior cingulate, and thalamus (Menon et al 1997). The P300 elicited in the auditory oddball paradigm likely comprises both P300a and P300b components, and their fronto-temporo-

parietal generators converge with many of the cortico-limbic brain structures implicated in the neuropathology of schizophrenia from both neuroimaging (for reviews, see Marsh et al 1996; Shenton et al 1997) and postmortem studies (e.g., Benes 1991; Rajkowska et al 1998; Selemon et al 1995). In addition, the putative neuroanatomical generators of P300 overlap with several of the brain regions shown to exhibit progressive volume decline in longitudinal MRI studies of schizophrenia, including the frontal lobe (Gur et al 1998; Mathalon et al, in press) as well as the temporal lobe and hippocampus (DeLisi et al 1995; Gur et al 1998; Jacobsen et al 1998; Mathalon et al, in press). Thus, both ERP and MRI data provide converging evidence regarding the brain regions implicated in the neuropathology of schizophrenia and its possibly progressive pathophysiology.

There are several limitations of the present study. First, although our hypotheses regarding progression in schizophrenia are fundamentally longitudinal, the present study was cross-sectional and therefore only suggestive of longitudinal processes. Cross-sectional designs address neurodegeneration in schizophrenia *in vivo* by correlating disease duration or chronological age with brain structure, brain function, or both. Such relationships can be difficult to detect, because individual differences often contribute more to the variance of a biological marker than the subtle effects of age or illness duration. The present findings suggesting that P300 may provide a marker of progressive brain changes in schizophrenia must await confirmation by longitudinal data. In addition, longitudinal data are needed to disentangle the effects of current age, age at onset, and illness duration, as these variables are often intercorrelated (Frangou et al 1997; O'Donnell et al 1995; Olichney et al 1998).

Second, our sample was quite heterogeneous with respect to symptom severity, medication status, and past history of alcohol abuse or dependence. Nonetheless, current symptomatology, medication status, and past alcohol history did not account for the effects of age, onset age, or illness duration on P300. Third, the assessment of duration of illness depends on the accurate determination of the age at illness onset, which in our case was defined retrospectively as the age at which DSM-III-R criteria for schizophrenia were met, based on the SCID interview. Retrospective assessments such as this are subject to recall bias, and other definitions may yield different results (Maurer and Hafner 1995). The measurement error associated with age at onset assessments may be a major contributor to the inconsistencies in the literature regarding relationships between illness onset and illness duration and other clinical and biological variables. Fourth, these data and conclusions can only be generalized to men with schizophrenia because women with schizophrenia may

differ from men in their course of illness and in brain pathology (Goldstein and Tsuang, 1990; Marsh and Casper, 1998).

Although the present results are suggestive of progressive functional brain changes over the schizophrenic illness course, they do not address the possible mechanisms underlying such progression. The contribution of cumulative medication, repeated hospitalizations, or even the toxic effects of psychosis (Wyatt 1991) to the reduction and slowing of P300 latency all need to be considered. Some studies suggest that medication may increase P300 amplitude in schizophrenia (e.g., Coburn et al 1998; Josiassen et al 1984; Roth et al 1979; Umbricht et al 1998), whereas other studies suggest that medication has no appreciable effect on P300 amplitude (Ford et al 1994c; Pass et al 1980; Pfefferbaum et al 1989; Roth et al 1981). Similarly, some studies suggest a role for medication in P300 latency prolongation in schizophrenia (Hirayasu et al 1998), whereas in a longitudinal study others have concluded that medication may even shorten P300 in schizophrenic patients (Ford et al 1994c). The roles of clinical symptomatology and severity, as well as medication, in the progression or stability of the neuropathological processes in schizophrenia can only be elucidated in prospective longitudinal studies in which functional brain markers such as P300 amplitude and latency, as well as structural markers such as volumetric quantitative MRI, are followed over time.

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