P300 Amplitude is Related to Clinical State in Severely and Moderately Ill Patients with Schizophrenia

Judith M. Ford, Daniel H. Mathalon, Laura Marsh, William O. Faustman, Debra Harris, Anne L. Hoff, Michael Beal, and Adolf Pfefferbaum

Background: *Relationships between illness severity and neurobiologic abnormalities in schizophrenia were studied in subpopulations varying in clinical severity.*

Methods: *Auditory ERPs were collected from 28 severely ill, chronically hospitalized schizophrenic men from a state hospital; 29 moderately ill inpatient and outpatient schizophrenic men from a veterans hospital; and 30 healthy male subjects from the community as controls. Clinical symptoms were evaluated in patients using the Brief Psychiatric Rating Scale (BPRS).*

Results: *Both schizophrenic patient groups had smaller P300 amplitude than the control subjects. Severely ill patients had smaller P300s than moderately ill patients and scored higher on three BPRS factor scores as well as BPRS Total. Among severely ill patients, P300 amplitude was unrelated to clinical symptoms. Among moderately ill patients, P300 was related to Withdrawal/Retardation, Anxiety/Depression, and BPRS Total. After combining patients, Thinking Disturbance emerged as an additional correlate of P300. Group differences in P300 could not be accounted for by group differences in symptom severity using analysis of covariance.*

Conclusions: *Reduced P300 amplitude marks the diagnosis of schizophrenia, but also reflects individual differences in severity, including positive symptoms. Previous failures to find relationships between positive symptoms and P300 may have been due to a restricted range of clinical severity.* Biol Psychiatry 1999;46:94–101 © *1999 Society of Biological Psychiatry*

Key Words: Schizophrenia, event-related potentials (ERPs), P300, clinical symptoms

Introduction

The auditory P300 component of the event-related brain potential (ERP) is reliably reduced in schizophrenia (Ford et al 1992), even in patients stabilized on medication (Pass et al 1980; Pfefferbaum et al 1989; Roth et al 1981), in first episode patients (Salisbury et al 1998), and when patients are retested after an interval of 1 year (Turetsky et al 1998). This suggests that P300 amplitude provides a neurobiologic marker for the enduring nature of the disease. A further question is whether among patients with schizophrenia, P300 amplitude can also vary with fluctuations in clinical state. Several clinical cross-sectional studies have reported associations between P300 amplitude and the severity of negative symptoms (Mathalon et al 1998; Pfefferbaum et al 1989; Pritchard 1986), fewer have reported associations between P300 amplitude and positive symptoms (Juckel et al 1996).

One reason for the stronger associations found between P300 and negative symptoms than between P300 and positive symptoms may be the more enduring, trait-like nature of negative, relative to positive, symptoms in schizophrenia (Mathalon and Pfefferbaum 1997; Mueser et al 1991; Pfohl and Winokur 1982; Putnam et al 1996). However, positive symptoms, though more variable over time within patients, also characterize trait-like individual differences between patients. Recently, we showed that although associations between positive symptoms and P300 could not be detected between subjects at a single time point, within-subject variations in P300 amplitude over multiple observations were related to variations in positive symptom states (Mathalon et al 1998). At issue is whether a relationship between P300 and positive symptoms can be demonstrated cross-sectionally, indicating the sensitivity of this neurobiologic measure to more enduring individual differences in positive symptoms.

Another reason for difficulty in detecting any association between P300 and positive symptoms could be a restricted range of values, both clinical and neurobiologic, among the patients included in the analysis. Sampling patients from different clinical settings, which cater to patients differing in long-term clinical severity, may in-

From the Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA (JMF, DHM, LM, WOF, AP); Psychiatry Service, Veterans Affairs, Palo Alto Health Care System, Palo Alto, CA (JF, DHM, WOF); Department of Psychiatry, University of California at Davis, Davis, CA (ALH); University of California at Davis-Napa Research Center, Napa State Hospital, Napa, CA (DH, ALH, MB); Department of Psychiatry (current affiliation), University of California at San Francisco, San Francisco, CA (DH); and Neuropsychiatry Program (current affiliation), SRI International, Menlo Park, CA (AP); Department of Psychiatry and Behavioral Science, Johns Hopkins Hospital, Baltimore, MD (LM).

Address reprint requests to Judith M. Ford, Ph.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5550.

Received June 5, 1998; revised August 20, 1998; accepted August 26, 1998.

0006-3223/99/$20.00
PII S0006-3223(98)0290-X

Table 1. Demographic, Neurophysiologic and Clinical Measures for Severely Ill and Moderately Ill Schizophrenics and Control Subjects

	Severely Ill (SI) ($n = 28$)			Moderately Ill (MI) ($n = 29$)		[1]SI vs Cont [2]MI vs Cont	Control Subjects ($n = 30$)	
	Mean	SD	SI vs MI	Mean	SD		Mean	SD
Demographics								
Age	34.1	7.7		36.7	4.6		36.9	6.7
Years of Education	10.2	3.1	d,e	12.9	1.5	[1&2]e	16.0	2.4
Neurophysiology								
N1 Amplitude at C_z (μV)	−4.13	2.38		−4.96	3.25	[1&2]e	−8.49	2.44
N1 Latency at C_z (msec)	107.14	20.92		107.62	18.19		110.4	16.09
P300 Amplitude at P_z	4.98	2.92	b,e	7.55	3.9	[1&2]e	11.54	4.79
P300 Latency at P_z (msec)	378.75	82.84		363.24	52.51		349.83	51.47
Clinical Features								
BPRS Total	55.18	12.32	d	40.60	8.58			
Withdrawal/Retardation	9.39	2.83	b	7.55	2.39			
Thinking Disturbance	12.71	4.47	d	8.40	2.30			
Anxiety/Depression	6.53	2.47		7.03	2.44			
Hostility/Suspiciousness	10.07	3.19	c	7.09	3.28			
Age of Onset (years)	16.54	4.72	d	23.31	5.11			
Disease Duration (years)	17.57	6.82	b	13.34	6.32			

1-tailed t-test comparisons a $p < .05$, b $p < .01$, c $p < .001$, d $p < .0001$, Scheffe post hoc e $p < .05$.

crease the chance that single cross-sectional measurements will reflect not only variation in current clinical state but will also capture a broader range of enduring individual differences. This increase in trait-related variance would facilitate the demonstration of an association between clinical and neurobiologic variables, even with cross-sectional data. For example, associations between brain dysmorphology and symptom severity, not seen when groups of patients differing in severity of illness were analyzed separately, has recently been demonstrated by pooling data across both groups (Marsh et al 1999).

The earlier N1 component is also reduced in patients with schizophrenia (Bruder et al 1996; Ford et al 1994b; Pfefferbaum et al 1989; Roemer and Shagass 1990; Roth et al 1991), and according to a recent report, this reduction may be due to the disorganized/undifferentiated patients in the samples studied (Boutros et al 1997). There have been few attempts to relate N1 reduction to clinical symptoms, although Laurent and Baribeau (1992) found N1 was related to thinking disturbance.

The aims of the present study were to determine 1) whether N1 and P300 differentiate between two groups of schizophrenic patients known to differ in clinical severity; and 2) whether N1 and P300 are related to symptom severity across all patients. Specifically, we hypothesized that more severely ill patients would have smaller N1 and P300 amplitudes and that amplitude reductions would be related to more severe symptoms. Because of the directional nature of our hypotheses, we used one-tailed tests of statistical significance. We elicited ERPs to target tones in an auditory oddball paradigm from two groups of patients with schizophrenia: moderately ill patients from the Veterans Affairs Palo Alto Health Care System and severely ill inpatients from Napa State Hospital, and an age-matched group of healthy control subjects.

Methods and Materials

Patients

Demographic and clinical characteristics of the subject groups are provided in Table 1. Written informed consent was obtained from all subjects or their guardians. Patients all participated in a standard auditory oddball ERP paradigm when they had been stable for at least 2 weeks on either typical or atypical antipsychotic medication. Patient assessment procedures and inclusion and exclusion criteria are provided in earlier reports on structural brain characteristics in these patients (Lim et al 1996; Marsh et al 1997; Sullivan et al 1998; Zipursky et al 1992; Zipursky et al 1994). Patients were medically healthy men who met diagnostic criteria for chronic schizophrenia according to the Diagnostic and Statistical Manual-III-Revised (DSM-III-R) (American Psychiatric Association 1987). Patients with a history of significant head injury (loss of consciousness ≥ 30 min or neurologic sequelae), current alcohol or substance dependence, past or present epilepsy, psychosurgery or other nonschizophrenic illness that would affect the central nervous system, and those aged over 45 years were excluded from the analysis.

Moderately ill patients included both acute in-patients ($n = 22$) on a research psychiatric ward at the Veterans Administration Palo Alto Health Care System and out-patients ($n = 7$) at the same facility. They all had sufficiently good physical and mental premorbid histories to qualify for military service, and now lived in the community. Severely ill patients ($n = 28$) were recruited from locked in-patient wards at Napa State Hospital. They required chronic institutionalization, primarily because of severe psychotic symptomatology that responded only partially to neuroleptic treatment. Most patients were clinically ill by age 20 years, which disrupted their formal education. All but one were legally conserved.

Control subjects for this study included men recruited from the neighboring community. Some had participated previously in other electrophysiologic (Ford et al 1994a; Ford et al 1994b) studies from our laboratory. Subjects who responded to recruitment advertisements were initially screened over the phone. Those willing to participate and passing this screen were invited into the laboratory where they were further screened by a psychiatric interview [Schedule for Affective Disorders and Schizophrenia - Lifetime (SADS-L), Endicott and Spitzer 1978, or Structured Clinical Interview for DSM-III-R (SCID), Spitzer et al 1989]. Prospective control subjects were excluded if they met criteria for substance abuse in the past year, or life-time history of other psychiatric disorder.

DISEASE DURATION. Duration of disease was estimated as the difference between age at onset of schizophrenia and age at testing. For severely ill patients, age at onset was defined as the age at which reliable evidence from records or interviews indicated presence of at least two of the DSM-III-R Section A diagnostic criteria for schizophrenia. For moderately ill patients, age at onset (symptoms of schizophrenia first present for 6 months, with an active phase of at least 1 week) was estimated from patient interviews with the exact age established by consensus between the attending physician who performed a clinical interview and an interviewer who administered the SCID.

CLINICAL SYMPTOM ASSESSMENT. Patients were assessed using the Brief Psychiatric Rating Scale (BPRS) usually on the same day or within a day of ERP testing. Ratings were done by two trained raters, with the average of their ratings being used. The BPRS is a clinician-rated instrument based on a semistructured interview yielding measures of symptomatology on 18 items that have been the subject of extensive factor-analytic study (Hedlund and Vieweg 1980; Overall et al 1967). In addition to the total score on the BPRS, we also used 4 factor scores computed to 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) (Table 1).

ERP Recording and Analysis

Both groups of patients were tested on an auditory oddball paradigm which took about 10 min to conduct and consisted of a series of 320 standard tones and 80 target tones with a fixed interstimulus interval of 1.5 sec. Standard tones were 500 Hz, 70 dB SPL, 50 msec duration and occurred on 80% of the trials. Target tones were 1000 Hz, 70 dB SPL, 50 msec duration and occurred on 20% of the trials. Tones had a shaped rise and fall time of 5 msec. Stimuli were presented in a Bernoulli sequence held constant across subjects. Subjects were asked to press a reaction time button with their preferred hand to the target tones, giving equal importance to speed and accuracy.

EEG recorded from F_z, C_z, P_z, O_z, A_1, T_3, C_3, C_4, T_4, and A_2 electrodes was referenced to a sternovertebral electrode with a balancing circuit to minimize EKG artifacts (Stephenson and Gibbs 1951). Vertical EOG was recorded from electrodes placed above and below the right eye, and horizontal EOG from electrodes placed at the outer canthi 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 ($>\pm 250$ μV) were rejected. Next, single trials at each electrode were individually corrected for the effects of eye blinks and eye movements (Gratton et al 1983; 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 0.5 Hz (down 3 dB) high pass filter (Coppola 1979) and with a 12.4 Hz (down 3 dB) low pass filter (Ruchkin and Glaser 1978). For the analyses presented here, P300 was measured as the most positive peak at F_z, C_z, and P_z between 280 and 600 ms and N1 was measured as the most negative peak between 50 and 150 msec at C_z.

Statistical Analysis

Statistical analysis proceeded in three steps: 1) One-way analysis of variance (ANOVA) was performed using factors of group (controls, severely ill schizophrenics, moderately ill schizophrenics) for demographic and clinical variables, with follow-up *t* tests where group effects were significant. 2) Repeated measures ANOVA (group and midline electrode site) was performed for P300 amplitudes with post hoc Scheffe tests conducted at each site if the group × site interaction was significant. A similar ANOVA was performed for N1 without the electrode site factor. 3) Regression analyses were performed to determine the relationship between clinical variables and ERP amplitudes within severely ill and moderately ill subgroups separately, as well as across combined samples. 4) Clinical variables, for which slopes of the linear regression with ERP values did not differ between groups, were subjected to an analysis of covariance (ANCOVA) to determine whether they accounted for any group difference in the ERP values.

Results

Group Comparisons

The more severely ill patients had higher scores on three of the four BPRS factor scores (Thinking Disturbance,

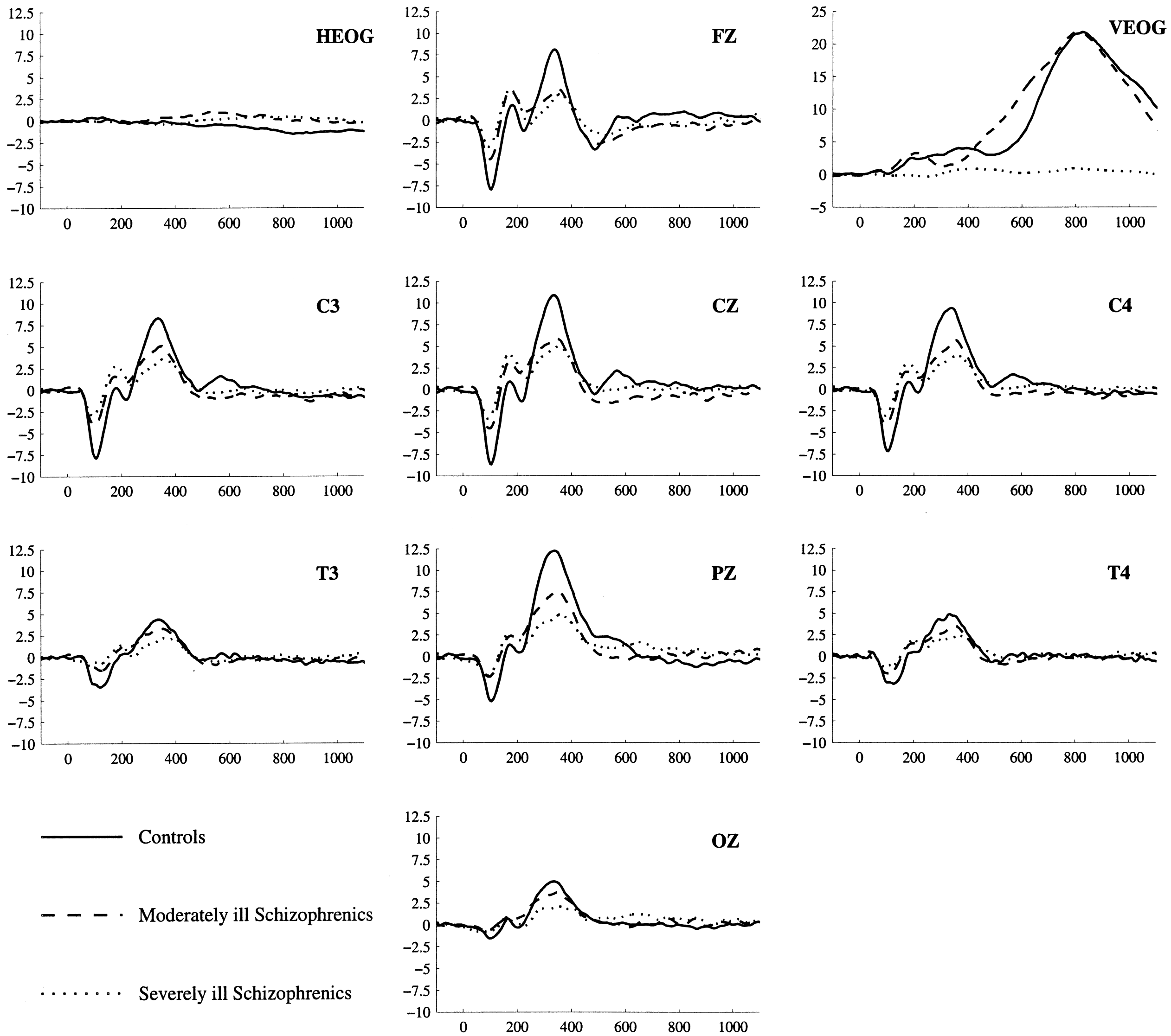

Figure 1. Grand averages of normal controls ($n = 30$) (solid line), moderately ill schizophrenics ($n = 29$) (dashed line), and severely ill schizophrenics ($n = 28$) (dotted line) for ERPs elicited to target tones. Y-axis = microvolts; X-axis = milliseconds.

Withdrawal/Retardation, and Hostility/Suspiciousness), as well as a higher BPRS Total score than the moderately ill patients. In addition, they had been ill longer and had less formal education (Table 1).

Grand average ERPs are overlaid for the two patient groups and the normal controls in Figure 1. The group effect for P300 amplitude across midline sites was significant [$F(2,84) = 15.33$, $p < .0001$], as was the site effect [$F(2,168) = 44.39$, $p < .0001$], with a group by site interaction [$F(4,168) = 3.64$, $p < .007$]. Post hoc analyses revealed significant differences in P300 amplitude between the severely ill and control groups at F_z [Scheffe $F = 11.27$], C_z [Scheffe $F = 9.2$], and P_z [Scheffe $F = 19.72$]; and between moderately ill and controls groups at F_z [Scheffe $F = 5.76$], C_z [Scheffe $F = 5.10$], and P_z [Scheffe $F = 7.41$]. P300 was significantly smaller in severely ill than moderately ill schizophrenics only at P_z [Scheffe $F = 7.87$, $p < .01$]. The effect of group membership and midline scalp site on P300 amplitude can be seen in Figure 2. This interaction remained significant after P300 amplitude normalization (McCarthy and Wood 1985) [$F(4,168) = 2.91$, $p < .03$].

The group effect for N1 amplitude was significant [$F(2,84) = 21.33$ $p < .0001$]. Post hoc analyses revealed significant differences in N1 amplitude between the severely ill and the control groups [Scheffe $F =$

18.68], between the moderately ill and control groups [Scheffe $F = 12.43$], but not between severely ill and moderately ill patients.

ERP Clinical Relationships

The regression of P300 amplitude on disease duration revealed no significant relationship between these variables either in each schizophrenic group separately, or when they were combined. Within the severely ill schizophrenic group alone, P300 amplitude was unrelated to any of the BPRS factor scores, or BPRS Total (p values ranged from .07 for Hostility/Suspiciousness to .49 for BPRS Total). Within the moderately ill schizophrenic group alone, P300 amplitude was significantly related to Withdrawal/Retardation [$r = -.50$, $p < .003$], Anxiety/Depression [$r = -.42$, $p \leq .01$], and BPRS Total [$r = -.32$, $p < .05$], but was unrelated to Thinking Disturbance ($p = .44$) or Hostility/Suspiciousness ($p = 0.12$). When data from both groups were pooled, however, patients with smaller P300 amplitudes had higher scores for BPRS Total [$r = -0.32$, $p < .01$], Withdrawal/Retardation [$r = -.28$, $p < .02$], and Thinking Disturbance [$r = -.26$, $p < .03$] (Figure 3). Polynomial regression analyses revealed no significant quadratic or cubic relationships between P300 and clinical variables in the combined group. Nonparametric Spearman correlations yielded the same results.

Parallel analysis for N1 at C_z reveals a different pattern of association with clinical variables to that seen for P300, perhaps because N1 did not differentiate the clinical groups. There was no association between N1 amplitude and disease duration for either group, singly or combined. There was no relationship between N1 amplitude and any of the BPRS factor scores, or BPRS Total within the severely ill schizophrenic group alone. However, within the moderately ill schizophrenic group alone, smaller (i.e., less negative) N1 amplitudes were significantly related to greater Withdrawal/Retardation [$r = .50$, $p < .003$], Anxiety/Depression [$r = 0.47$, $p < .008$], and BPRS Total [$r = .41$, $p < .015$]. N1 tended to be related to Thinking Disturbance ($r = .28$, $p = .07$), but not Hostility/Suspiciousness ($p = .19$). Pooling data across both groups strengthened the relationship between smaller N1 amplitudes and higher Thinking Disturbance [$r = .28$, $p < .02$], relative to the trend observed in the moderately ill group alone, maintained the relationships with BPRS Total ($r = .23$, $p \leq .04$) and Withdrawal/Retardation ($r = .24$, $p < .04$), but attenuated the relationship with Anxiety/Depression ($r = .18$, $p < .09$).

Although N1 and P300 were moderately correlated ($r = -.49$, $p < .0001$), we attempted to assess their independent contributions to the prediction of clinical symptom scores using multiple linear regression analyses. When each of the four BPRS factor scores were individually regressed on both N1 and P300, neither one significantly predicted clinical symptoms after controlling for the other. However, when BPRS Total was regressed on

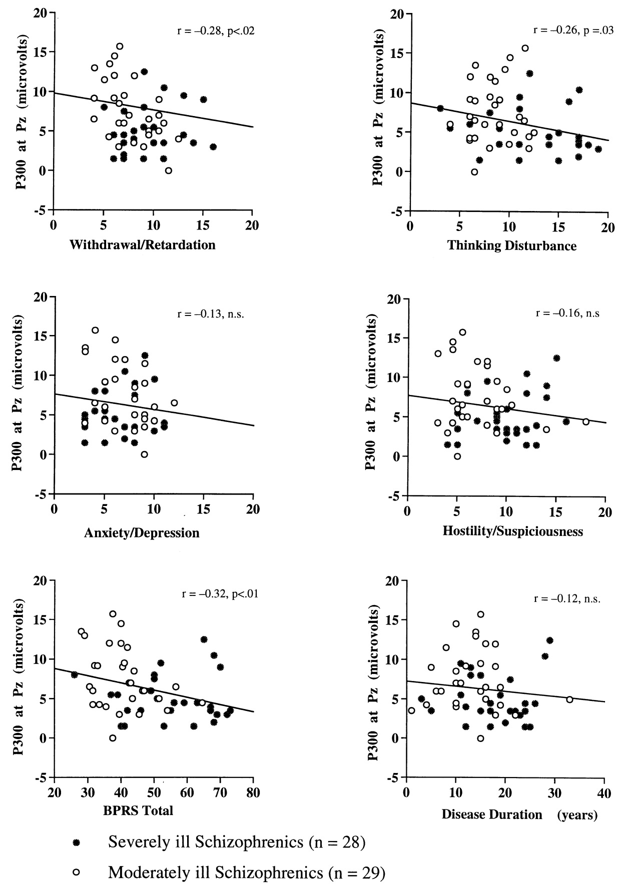

Figure 3. Relationships between P300 amplitude, the four BPRS factor scores, BPRS Total, and disease duration for 28 severely ill and 29 moderately ill schizophrenic patients. Pooled group regression lines are shown. One-tailed significance levels are shown.

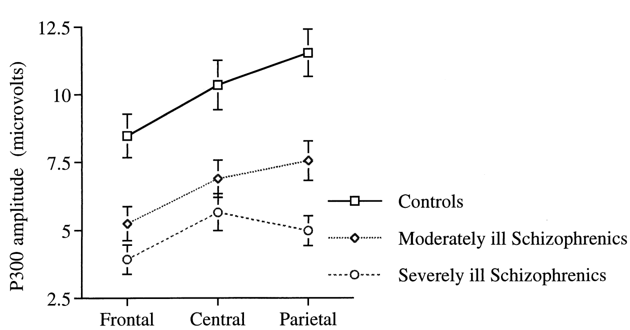

Figure 2. Means and standard errors for P300 amplitude from three midline leads F_z, C_z, and P_z, for control subjects, severely ill patients, and moderately ill patients.

the two ERP components, P300 ($\beta = -.26$, $p < .05$, one-tailed) but not N1 ($\beta = .11$, n.s.) emerged as a significant independent predictor. Thus, the four symptom factors individually depended on variance that was shared by N1 and P300; however, when these symptoms were taken additively and broadened with additional symptomatology items (BPRS Total), P300, but not N1, accounted for unique variance in clinical severity.

Clinical Variables Accounting for Group P300 Differences

For clinical variables with a linear relationship to P300 amplitude that did not have different slopes between groups, an ANCOVA was performed using that clinical variable and group to predict P300 amplitude. Significant P300 group differences persisted, even after accounting for Thinking Disturbance [$F(1,54) = 4.11$, $p < .025$], Hostility/Suspiciousness [$F(1,54) = 6.18$, $p < .01$], disease duration [$F(1,54) = 6.92$, $p < .01$], and BPRS Total [$F(1,54) = 2.81$, $p < .05$]. This analysis was not performed for Withdrawal/Retardation and Anxiety/Depression because the linear slopes of these variables with P300 were significantly different in the two patient groups. N1 was not subjected to this analysis because N1 did not differ across groups.

The contribution of education to differences in P300 between severely ill and moderately ill schizophrenic groups was assessed using ANCOVA. Group differences in P300 persisted even when years of education data was entered as a covariate [$F(2,53) = 4.57$, $p < .01$]. Note, years of education was not associated with P300 amplitude within the moderately ill patients ($p < .55$), the severely ill patients ($p < .55$), or with the groups combined ($p < .20$).[1]

Discussion

P300 amplitude is a neurobiologic measure recorded from the scalp of individuals engaged in specific tasks. For this study, the task was a simple target detection task. In studies using this paradigm in healthy subjects, P300 amplitude is sensitive not only to variables that are state/task-dependent, such as attention and stimulus probability (Duncan-Johnson and Donchin 1977; Johnson 1987), but also to variables that are more stable and enduring, such as a cortical gray matter volume (Ford et al 1996). In longitudinal studies of psychiatric patients, P300 is sensitive to state fluctuations in positive symptoms (Mathalon et al, unpublished data 1999), individual differences in more enduring negative symptoms (Mathalon et al, unpublished data 1999), and to the stable diagnosis of schizophrenia, irrespective of clinical state (Mathalon et al, unpublished data 1999; Turetsky et al 1998).

Among the severely ill patients, P300 was unrelated to any symptom dimension; whereas among the moderately ill patients, relationships with BPRS Total, Withdrawal/Retardation, and Anxiety/Depression attained significance, consistent with previous reports of P300 amplitude reflecting negative symptoms (Blackwood et al 1987; Kemali et al 1988; Pfefferbaum et al 1989; Strik et al 1993; Ward et al 1991). The lack of relationship within the severely ill group compared to the moderately ill group might be because of the restricted range of P300 amplitudes available; 74% of the sample had P300 amplitude < 6 μV, compared with only 43% in the moderately ill group. When data were pooled across groups, relationships of P300 amplitude with Withdrawal/Retardation, Thinking Disturbance, and BPRS Total were observed. The relationship with Thinking Disturbance demonstrates that although P300 amplitude was not sensitive to positive symptoms within groups, it was sensitive to this positive symptom factor when patients from groups differing in clinical severity were combined. It is possible that earlier failures to demonstrate a relationship between P300 and positive symptoms cross-sectionally is due, in part, to a restriction of range in symptom severity.

In this cross-sectional analysis, we found that P300 recorded at P_z is smaller in severely ill than similarly aged moderately ill schizophrenic patients. Although the severely ill patients were significantly more symptomatic than the moderately ill patients, neither overall severity of illness (as measured by BPRS Total), nor individual factor scores, could completely account for the P300 amplitude differences between groups. While associations between symptom severity and P300 amplitude were uncovered, none of these associations on their own were able to account completely for group differences in P300 amplitude. The severely ill patients had longer disease durations than the moderately ill patients, but this did not account for the P300 amplitude differences between groups.[2] The groups also differed in years of formal education, and by inference, perhaps cognitive ability. Because relationships between neuropsychological deficits and negative symptoms have been reported (Braff et al 1991; Miller et al 1993), neuropsychological deficits might contribute independently of symptoms to the smaller P300s observed in more severely ill patients. Years of education as an indicator of cognitive abilities provided no support to this possibility, however, analysis using a more direct assess-

[1] Because there are no reports in the literature relating P300 to education, these tests were two-tailed.

[2] The extent to which reported group differences in age of onset can be attributable to differences in criteria for defining age of onset used by the two hospitals is unknown. This limitation should be born in mind when evaluating this observation.

ment of cognitive ability is needed to fully resolve this issue.

Reduction in N1 seen in the patients compared to the controls is consistent with the literature (Bruder et al 1996; Ford et al 1994b; Pfefferbaum et al 1989; Roemer and Shagass 1990; Roth et al 1991). Despite the fact that N1 did not differentiate the two patient groups, N1 amplitude became sensitive to Withdrawal/Retardation, BPRS Total, and Thinking Disturbance, when data from both groups were combined, the latter replicating an earlier finding (Laurent and Baribeau 1992). Despite the fact that N1 and P300 shared approximately 25% of their variance, only P300 emerged as an independent predictor of BPRS Total scores. Thus, P300 may be more reflective of general clinical severity than N1.

Clinical severity differences observed between these groups of patients underscore the fact that any single clinical population may not encompass the full range of symptom severity for this disease. Relationships between clinical symptoms and biologic variables may only emerge when the full clinical range is present. Variables such as cortical gray matter (Ford et al 1996) might also be relevant as a predictor of reduced P300 amplitude in schizophrenia. These findings also suggested that the two groups of patients differed along a continuum of severity and along a continuum of P300 amplitudes.

The scalp distribution of P300 in the severely ill schizophrenic patients did not show the parietal maximum seen in control subjects and moderately ill schizophrenic patients. The centrally maximal distribution seen in the severely ill schizophrenic patients is often also seen in healthy elderly subjects (Ford and Pfefferbaum 1991) and in responses elicited by a “no-go” stimulus (Pfefferbaum and Ford 1988). Differences in P300 scalp distribution in healthy subjects have been used as indicators for activation of different neural processes (Rösler et al 1995a; Rösler et al 1995b). The extent to which such interpretations are applicable to these severely ill schizophrenic patients awaits further testing.

This work was supported by the National Institute of Health [MH30854 (AP), MH53485 (LM), MH40052 (JF)]; the Department of Veterans Affairs; the Norris Foundation; Stanford University; the California Department of Mental Health; and Napa State Hospital.

These data were reported in part at the meeting of the Biological Psychiatry Society, May, 1997, San Diego, CA.

We thank the staff at the Department of Veterans Affairs (VA) Palo Alto Health Care System, the Stanford/VA Mental Health Clinical Research Center, and Napa State Hospital for facilitating patient participation; Kyungtak Minn, MD and Kelvin O. Lim, MD, for clinical assistance; Patricia M. White, Brandy Isaacks, Daren Jackson, Clarine Bell, Shamini Jain, and Jennifer Hoffman for testing the patients; and Margaret Rosenbloom for preparing the manuscript.

References

American-Psychiatric-Association (1987): *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. Washington: American Psychiatric Association.

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. *Brit J Psychiatry* 150:154–160.

Boutros N, Nasrallah H, Leighty R, Torello M, Tueting P, Olson S (1997): Auditory evoked potentials, clinical vs. research applications. *Psychiatry Res* 69:183–195.

Braff DL, Heaton R, Kuck J, et al (1991): The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Arch Gen Psychiatry* 48:891–898.

Bruder GE, Tenke CE, Rabinowics E, et al (1996): Electrophysiologic studies of brain activity in schizophrenia. In: Kaufman CA, Gorman JM, editors. *Schizophrenia: New Directions for Clinical Research and Treatment*. Larchmont, NY: Mary Ann Libert, Inc, pp 17–33.

Coppola R (1979): Isolating low frequency activity in EEG spectrum analysis. *Electroencephalogr Clin Neurophysiol* 46:224–226.

Duncan-Johnson CC, Donchin E (1977): On quantifying surprise: The variation in event-related potentials with subjective probability. *Psychophysiology* 14:456–467.

Endicott J, Spitzer RL (1978): A diagnostic interview: The schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 35:837–844.

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, pp 916–921.

Ford JM, Pfefferbaum A (1991): Event-related potentials and eyeblink responses in automatic and controlled processing: Effects of age. *Electroencephalogr Clin Neurophysiol* 78: 361–377.

Ford JM, Roth WT, Pfefferbaum A (1992): P3 and schizophrenia. *Annals of the NY Academy of Sciences* 658:146–162.

Ford JM, White P, Lim KO, Pfefferbaum A (1994a): Schizophrenics have fewer and smaller P300s: A single-trial analysis. *Biol Psychiatry* 35:96–103.

Ford JM, White PM, Csernansky J, Faustman W, Roth WT, Pfefferbaum A (1994b): ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 36:153–171.

Gratton G, Coles MGH, Donchin E (1983): A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 55:468–484.

Hedlund JL, Vieweg BW (1980): The Brief Psychiatric Rating Scale (BPRS): A comprehensive review. *J Operational Psychiatry* 11:48–64.

Johnson R (1987): The amplitude of the P300 component of the event-related potential: Review and synthesis. In: Ackles PK, Jennings JR, Coles MGH, editors. *Advances in Psychophysiology, Vol 3*. Greenwich, CT: JAI Press, pp 69–137.

Juckel G, Muller-Schubert A, Gaebel W, Hegerl U (1996): Residual symptoms and P300 in schizophrenic outpatients. *Psychiatry Res* 65:23–32.

Kemali D, Galderisi S, Maj M, Mucci A, Cesarelli M, D'Ambra L (1988): Event-related potentials in schizophrenic patients: Clinical and neurophysiological correlates. *Res Commun Psychol Psychiatry Behav* 13:3–16.

Laurent JP, Baribeau J (1992): AERPs and clinical evolution of thought disorders over five years. *Int J Psychophysiol* 13: 271–282.

Lim KO, Harris D, Beal M, et al (1996): Gray matter volume deficits in young onset schizophrenia are independent of age of onset. *Biol Psychiatry* 40:4–13.

Marsh L, Harris D, Lim KO, et al (1997): Structural MRI abnormalities in adults with severe chronic schizophrenia and an early age at clinical onset. *Arch Gen Psychiatry* 54:1104–1112.

Marsh L, Lim KO, Hoff AL, et al (1999): Severity of schizophrenia and MRI abnormalities: A comparison of state and veterans hospital patients. *Biol Psychiatry* 45:49–61.

Mathalon DH, Pfefferbaum A (1997): Stability of symptoms in hospitalized schizophrenics (abs). *Biol Psychiatry* 41:99S.

McCarthy G, Wood CC (1985): Scalp distribution of event-related potentials: An ambiguity associated with analysis of variance models. *Electroencephalogr Clin Neurophysiol* 62: 203–208.

Miller D, Arndt S, Andreasen N (1993): Alogia, attentional impairment, and inappropriate affect: their status in the dimensions of schizophrenia. *Compr Psychiatry* 34:221–226.

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.

Overall JE, Hollister L, Pichot R (1967): Major psychiatric disorders. A four-dimensional model. *Arch Gen Psychiatry* 16:146–151.

Pass H, Klorman R, Salzman L, Klein R, Kaskey G (1980): The late positive component of the evoked response in acute schizophrenics during a test of sustained attention. *Biol Psychiatry* 15:9–20.

Pfefferbaum A, Ford JM (1988): ERPs to stimuli requiring response production and inhibition: The effects of age, probability and visual noise. *Electroencephalogr Clin Neurophysiol* 71:55–63.

Pfefferbaum A, Ford JM, White P, 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. *Brit J Psychiatry* 141:567–572.

Pritchard WS (1986): Cognitive event-related potential correlates of schizophrenia. *Psychol Bull* 100:43–66.

Putnam KM, Harvey PD, Parrella M, et al (1996): Symptom stability in geriatric chronic schizophrenic inpatients: A one-year follow-up study. *Biol Psychiatry* 39:92–99.

Roemer RA, Shagass C (1990): Replication of an evoked potential study of lateralized hemispheric dysfunction in schizophrenics. *Biol Psychiatry* 28:275–291.

Rösler F, Heil M, Bajric J, Pauls AC, Hennighausen E (1995a): Patterns of cerebral activation while mental images are rotated and changed in size. *Psychophysiology* 32:135–149.

Rösler F, Heil M, Hennighausen E (1995b): Distinct cortical activation patterns during long-term memory retrieval of verbal, spatial, and color information. *J Cog Neurosci* 7:51–65.

Roth WT, Goodale J, Pfefferbaum A (1991): Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. *Biol Psychiatry* 29:585–599.

Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS (1981): Auditory event-related potentials in schizophrenia and depression. *Psychiatry Res* 4:199–212.

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, pp 579–581.

Salisbury DF, Shenton ME, Sherwood AR, et al (1998): First episode schizophrenic psychosis differs from first episode affective psychosis and controls in P300 amplitudes over left temporal lobe. *Arch Gen Psychiatry* 55:173–180.

Spitzer RL, Gibbon M, Skodol AE, Williams JBW, First MB (1989): *DSM-III-R Casebook.* Washington, DC: American Psychiatric Press.

Stephenson WA, Gibbs FA (1951): A balanced non-cephalic reference electrode. *Electroencephalogr Clin Neurophysiol* 3:237–240.

Strik WK, Dierks T, Maurer K (1993): Amplitudes of auditory P300 in remitted and residual schizophrenics: Correlations with clinical features. *Neuropsychobiol* 27:54–60.

Sullivan E, Lim K, Mathalon D, et al (1998): A profile of cortical gray matter volume characteristic of schizophrenia. *Cereb Cortex* 8:117–124.

Turetsky B, Colbath EA, Gur RE (1998): P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change. *Biol Psychiatry* 43:31–39.

Ward PB, Catts SV, Fox AM, Michie PT, McConaghy N (1991): Auditory selective attention and event-related potentials in schizophrenia. *Brit J Psychiatry* 158:534–539.

Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A (1992): Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry* 49:195–205.

Zipursky RB, Marsh L, Lim KO, et al (1994): Volumetric MRI assessment of temporal lobe structures in schizophrenia. *Biol Psychiatry* 35:501–516.