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# Trait and State Aspects of P300 Amplitude Reduction in Schizophrenia: A Retrospective Longitudinal Study

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**Background:** *The P300 component of the auditory event-related brain potential (ERP) is consistently reduced in schizophrenia. Longitudinal data are examined to determine whether P300 amplitude is a trait marker of schizophrenia or a state marker tracking clinical fluctuations over time.*

**Methods:** *Schizophrenic men (DSM-III-R) (n = 36) received ERP and the Brief Psychiatric Rating Scale (BPRS) assessments on multiple occasions, at varying intervals, under varying medication states. Automatically elicited auditory P3a and effortfully elicited auditory and visual P3b amplitudes were assessed. Brief Psychiatric Rating Scale scores were regressed on P300 amplitude within patients using both multiple regression models and non-parametric analyses of individual patient slopes. Event related brain potentials in patients were compared to ERPs from 34 age-matched control men, and stability of P300 over time was estimated with intraclass correlations.*

**Results:** *P300 amplitude, regardless of elicitation method or sensory modality, tracked BPRS Total and positive symptom scores over time, decreasing with symptom exacerbations and increasing with improvements. In addition, effortful auditory and visual P3b amplitudes tracked negative symptoms, and automatic auditory P3a tracked depression-anxiety symptoms. When analyses were limited to unmedicated occasions, auditory P3a and P3b persisted in tracking BPRS Total scores, with additional tracking of positive symptoms by P3b and mood symptoms by P3a. Mean auditory and visual P3bs, averaged over all measurement occasions for each individual, were inversely related to mean negative symptoms. Auditory P3a and P3b, but not visual P3b, amplitudes were smaller in patients than control subjects, even when patients were least symptomatic. P300 amplitudes showed high test-retest reliability in control subjects and patients and moderate stability over time in patients.*

**Conclusions:** *Auditory, and possibly visual, P300 amplitudes track fluctuations in clinical state, but only auditory P300 amplitude is a trait marker of schizophrenia. Biol*

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**Key Words:** Schizophrenia, P300 amplitude, trait, clinical state, symptoms, longitudinal

## Introduction

The amplitude of the P300 component of the event-related brain potential (ERP) is reliably reduced in patients with schizophrenia (for reviews, see Ford 1999; Ford et al 1992; McCarley et al 1991; Pritchard 1986). Whether P300 amplitude reduction reflects the underlying “trait” of schizophrenia or a more severe clinical state has typically been investigated in cross-sectional studies where trait effects are assessed by comparing patients and control subjects, and state effects are assessed by correlating P300 amplitude with symptom ratings. Trait evidence is provided by myriad findings of auditory P300 amplitude reduction in schizophrenic patients compared to control subjects (Ford et al 1992), including treated patients whose symptoms have improved (Blackwood et al 1987; Coburn et al 1998; Hirayasu and Ogura 1996; Pass et al 1980; St. Clair et al 1989; Turetsky et al 1998) or largely remitted (Rao et al 1995), as well as first episode patients (Hirayasu et al 1998; Salisbury et al 1998). Indeed, studies showing P300 reduction in unaffected first-degree relatives of schizophrenic patients suggest that P300 may be a marker of genetic vulnerability to the disease (Blackwood et al 1991; Frangou et al 1997; Kidogami et al 1991; Roxborough et al 1993; but see Friedman and Squires-Wheeler 1994).

Evidence for P300 amplitude as a clinical state marker in schizophrenia is provided by cross-sectional studies showing that patients with more severe negative symptoms have smaller auditory P300s (Blackwood et al 1987; Eikmeier et al 1992; Ford et al 1999; Maurer et al 1990; Pfefferbaum et al 1989; Pritchard 1986; Strik et al 1993; Ward et al 1991), with some exceptions (e.g., Barrett et al 1986; Coburn et al 1998; Laurent et al 1993; Shenton et al 1989). Some studies (Kemali et al 1988; Pfefferbaum et al

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1989), but not others (Brecher and Begleiter 1983; Ford et al 1994c), have also reported this relationship with visual P300s. Less consistently, studies have found auditory P300 amplitudes to be inversely correlated with positive symptoms (e.g., Egan et al 1994; Laurent et al 1993; McCarley et al 1991; but for a report showing a direct relationship, see Shenton et al 1989), including formal thought disorder (Egan et al 1994; Juckel et al 1996; Levitt et al 1973; Roth et al 1981; Ward et al 1991).

Inconsistent reports of a relationship between P300 amplitude and clinical state in cross-sectional studies of schizophrenia may arise because the variance in P300 amplitude at a single time point reflects both trait and state influences. Stable trait influences on P300 amplitude may include not only schizophrenia itself, but also other genetic or constitutional sources of variance including brain structure (Ford et al 1994a, 1996; Knight et al 1989; McCarley et al 1993) or function, or even skull thickness (Pfefferbaum and Rosenbloom 1987). Thus, while P300 may fluctuate over time with clinical state in patients, and with attentional states and contextual demands in all individuals (Donchin and Coles 1988; Isreal et al 1980; Verleger 1988), it probably does so around each individual's characteristic P300 amplitude. For schizophrenic patients with characteristically small P300s, an improved clinical state may increase their P300 amplitudes; yet, their amplitudes may never exceed those from patients with characteristically large P300s, even when the P300s from these latter patients have been reduced by a clinical exacerbation. Thus, in cross-sectional studies of schizophrenia, trait-like individual differences in P300 amplitude are inherently confounded with state-dependent variation in P300, thereby attenuating any potential relationships of P300 with clinical state.

Longitudinal designs overcome this problem by allowing a direct investigation of whether P300 amplitude tracks clinical fluctuations within schizophrenic patients over time. Some prior longitudinal studies have found auditory P300 amplitude to be stable over time, despite significant clinical improvement, suggesting that a small auditory P300 is a trait marker of schizophrenia (Blackwood et al 1987; Duncan et al 1987; Ford et al 1994c; Juckel et al 1996; Maeda et al 1996; Schall et al 1998; Turetsky et al 1998); however, longitudinal data have also shown significant increases in P300 amplitude with antipsychotic treatment (Asato et al 1996; Coburn et al 1998; Hirayasu and Ogura 1996; Maeda et al 1996; Schall et al 1998; Umbricht et al 1998) and/or symptom improvement (Schall et al 1998; Turetsky et al 1998). Most of these studies include only two time points, limiting their power to detect correlations between changes in P300 and clinical state. Multiple observations over time can generate greater within-patient variance in P300 and clinical state,

increasing the likelihood of detecting significant covariation between them.

Although visual P300 amplitudes have generally been reported to be normal in schizophrenia (e.g., Duncan et al 1987; Ford et al 1994c; Pfefferbaum et al 1989), some longitudinal studies have shown visual P300 to increase with clinical improvement, leading to speculation that visual P300 amplitudes may be a clinical state marker in schizophrenia (Duncan et al 1987; Ford et al 1994c); however, in these studies, as well as in most of the prior longitudinal auditory P300 studies, the patients were assessed when unmedicated and again when medicated, confounding changes in clinical state with changes in medication status.

Disentangling the effects of clinical fluctuations from the effects of antipsychotic medication per se is of theoretical importance for identifying biological markers of clinical state. Evidence that antipsychotic medication does not exert primary effects on P300 amplitude independent of changes in clinical state derives from cross-sectional studies showing no differences in auditory P300 amplitudes in medicated versus unmedicated patients (Pass et al 1980; Pfefferbaum et al 1989; Roth et al 1981; St. Clair et al 1989), as well as from longitudinal studies showing a correlation between the amount of P300 amplitude change and the degree of clinical improvement with medication (e.g., Duncan et al 1987; Schall et al 1998; Turetsky et al 1998); however, some cross-sectional studies have shown increased P300 amplitudes in medicated relative to unmedicated patients (Josiassen et al 1984; Roth et al 1979), and some longitudinal treatment studies have shown antipsychotics to increase P300 amplitude independent of clinical improvement (Asato et al 1996; Coburn et al 1998; Hirayasu and Ogura 1996; Umbricht et al 1998), suggesting direct medication effects on P300. Thus, whether P300 amplitude increases with clinical improvement independent of antipsychotic medication effects, as would be required for a true state marker, remains unresolved.

In normal subjects, variations in both functional demands (Donchin and Coles 1988; Verleger 1988) and in brain structure (Ford et al 1994a; Knight et al 1989) can influence P300 amplitude. P300 amplitude increases with greater expenditures of attentional resources (Isreal et al 1980) and greater demands on memory updating (Donchin and Coles 1988). P300 may be evoked automatically in response to an attention-eliciting stimulus, such as an infrequent startling sound (Roth et al 1984) or novel sound (Knight 1984), or effortfully in response to an infrequent stimulus during an "oddball" target detection task (Johnson 1987). The distinction between automatically and effortfully elicited P300 has elucidated two overlapping P300 subcomponents with distinct neural generators and functional significance (Ford et al 1994a; Halgren et al

Table 1. Demographic Data for Control Subjects and Patients

Variable	Normal control subjects ( <i>n</i> = 34)			Schizophrenic patients ( <i>n</i> = 36)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	42.8	11.4	22-60	38.7	7.2	27-55
Education (years)	16.4	2.8	11-23	12.6	2.0	7-20
Age at Illness Onset (years)				24.7	8.1	11-55
Ethnicity (%)						
Caucasian	88			66		
African-American	3			19		
Hispanic	6			3		
Other	3			11		

1998). One subcomponent, the P3a, has a fronto-central scalp maximum and is thought to reflect automatic cognitive processes involved in orienting to infrequent novel or salient stimuli (Squires et al 1975). The other subcomponent, P3b, has a parietal scalp maximum and is thought to reflect effortful cognitive processes involved in detecting and responding to task-relevant infrequent stimuli (Squires et al 1975). P300s elicited in a standard oddball target detection task are likely to reflect both P3a and P3b subcomponents, with fronto-central and parietal distributions, respectively (Turetsky et al 1998).

The possibility that P3a and P3b are differentially sensitive to clinical state effects in schizophrenia received support in a recent study (Turetsky et al 1998) showing that P3a increased with improvement in auditory hallucinations, whereas P3b increased with improvement in delusional thinking and stably reflected enduring negative symptoms. This suggests that psychotic symptoms interfere with processes associated with both P3a and P3b by diverting limited attentional resources from both automatically orienting and effortfully directing attention to auditory stimuli. Importantly, these same data also demonstrated that schizophrenic patients have P300 amplitude deficits relative to controls that are relatively stable over time (Turetsky et al 1998). Thus, schizophrenia may exert both trait and state influences on P300, consistent with the fact that schizophrenia is characterized both by enduring structural and functional brain deficits (for review, see Marsh et al 1996) and fluctuating symptomatology (Ciompi 1980; Mathalon and Pfefferbaum 1997; Schuldberg et al 1990).

Here we present a retrospective analysis of cross-sectional and longitudinal data addressing both state and trait influences on auditory P3a and P3b and visual P3b amplitudes in schizophrenia. In this study, we employ multiple observations over time per patient, compare automatic (P3a) and effortful (P3b) processing of infrequent auditory stimuli, compare auditory and visual P3bs, and attempt to disentangle clinical effects on P300 from medication effects per se. We hypothesized that 1) effortful auditory and visual P3b amplitudes and automatic auditory P3a amplitude track clinical

fluctuations within schizophrenic patients over time, even after controlling for variation in medication status, and 2) auditory, but not visual, P300 amplitude reduction is an enduring trait of schizophrenia, as reflected by cross-sectional differences with normal control subjects as well as by indices of trait stability.

## Methods and Materials

### Subjects

Thirty-six male inpatients at the Veterans Affairs Palo Alto Health Care System who met DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia were tested on multiple occasions. Diagnoses were determined by consensus of a psychiatrist or psychologist conducting a semistructured interview and a research assistant administering the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al 1989). Patients with current DSM-III-R alcohol or drug dependence or abuse (<3 months before participation) were excluded. Three participants had a past history of alcohol dependence, with two of these also having a history of drug dependence; three had a past history of alcohol abuse; and three had a past history of drug abuse.

Thirty-four healthy men, recruited by newspaper advertisement and word-of-mouth, comprised the normal control group. All were screened with a psychiatric interview using either the Schedule for Affective Disorders and Schizophrenia-Lifetime (Endicott and Spitzer 1978) or the SCID. Exclusion criteria were DSM-III-R diagnoses of major psychiatric disorders and current abuse or past dependence on alcohol or drugs. In addition, all subjects (patients and control subjects) were excluded for a history of head injury resulting in loss of consciousness greater than 30 minutes; hearing deficits greater than 30 dB at 500, 1000, and 2000 Hz in their better ear; or a history of medical illness affecting the central nervous system. All participants gave informed consent prior to study participation. Data from some of these patients and control subjects have appeared previously (Ford et al 1994b, 1994c, 1999). Demographic data for patients and control subjects are presented in Table 1.

### Clinical Ratings

Patients were administered the Brief Psychiatric Rating Scale (BPRS) on the same day as (55 occasions), or within 2 (62

occasions), 5 (5 occasions), or 7 (1 occasion) days of ERP testing. The BPRS is a clinician-rated instrument based on a semistructured interview yielding measures of symptomatology on 18 items (Overall et al 1967). In addition to BPRS Total scores, we used 4 subscales (Thinking Disturbance, Hostility-Suspiciousness, Withdrawal-Retardation, and Anxiety-Depression) derived from factor analytic studies (Hedlund and Vieweg 1980). The BPRS was administered by two trained raters, and the averages of their ratings were used. Interrater reliabilities (intra-class correlations), adjusted by the Spearman-Brown Prophecy Formula for scores averaged over two raters (Anastasi 1982), ranged from .75 to .90.

### *Medication Status*

Patients were either medicated with typical or experimental (quetiapine, raclopride, zacopride) antipsychotic medications or were unmedicated (either a placebo or no antipsychotic medication) at each ERP test occasion, determined by their participation in clinical drug trials (Ford et al 1994c; Newcomer et al 1992; Small et al 1997) or, in some cases, by the regimen prescribed by their treating psychiatrist. Three patients medicated with zacopride were considered to be unmedicated because zacopride was determined not to have antipsychotic efficacy (Newcomer et al 1992). All patients ( $n = 28$ ) who had been tested at least twice while unmedicated were included in a separate analysis to control for medication effects.

### *Event-Related Brain Potential Recording*

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

**AUTOMATIC AUDITORY PARADIGM.** Each subject wore earphones, sat upright in an easy chair in a sound attenuated room, and was presented with 400 auditory stimuli at a fixed interstimulus interval of 1.5 sec. Frequent (80%) tones (500 Hz, 80-dB sound pressure level [SPL], 50-msec duration with a shaped 5-msec rise and fall time) and infrequent (20%) noise bursts (105-dB SPL broad band, 50-msec duration with a 100- $\mu$ sec rise and fall time) were presented in a Bernoulli sequence held constant across subjects. No task was assigned.

**EFFORTFUL AUDITORY PARADIGM.** This paradigm was identical to the automatic auditory paradigm, except a 1000-Hz, 80-dB SPL, 50-msec tone was substituted for the noise and 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, with minus signs appearing on 80% of the trials, and plus signs appearing on the other 20%. Stimulus duration was 200 msec.

### *Event-Related Brain Potential Data*

Electroencephalograms (EEGs) were recorded from 12 scalp sites (Ford et al 1994c), but only data from midline frontal (Fz)

and parietal (Pz) sites elicited by the infrequent stimuli are presented here. Vertical electro-oculograms (EOGs) recorded from electrodes placed above and below the right eye and horizontal EOGs from electrodes placed at the outer canthus of each eye were used to correct single trials at each electrode for the effects of eye blinks and eye movements (Gratton et al 1983; Miller et al 1988). Before peak identification, the EEGs were 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). We defined the P300 elicited at Fz by the startling noise in the automatic paradigm as P3a and the P300 elicited at Pz by the target stimuli in both auditory and visual effortful paradigms as P3b. Both P3a and P3b were identified as the most positive peak between 275–600 msec poststimulus. We sometimes refer to P3a and P3b simply as “P300” when the distinction is not germane; when relevant, we identify them by name, usually along with their eliciting paradigm (automatic versus effortful).

### *Task Performance*

Trials with button presses occurring in the first 100 msec or after 1150 msec poststimulus were excluded, as were those with no button press. Reaction time (RT) and the number of incorrect button presses were quantified from the two effortful ERP paradigms and correlated with clinical state and P300 measures.

### *Longitudinal Testing Schedule*

Patients were tested on 2–7 different occasions while hospitalized. The timing and frequency of these occasions were determined mainly by experimental drug treatment protocols, but sometimes by the naturalistic course of the patient’s illness, and occurred at intervals ranging from 4 to 1061 days (mean interval =  $81.8 \pm 187.5$  days). Table 2 summarizes the number of occasions per patient for each ERP paradigm. Each occasion involved ERP testing on two consecutive days and a BPRS rating. Mean values of P300 over the two consecutive day test sessions were used to increase reliability. Test days yielding <20 of the possible 80 infrequent trials after artifact and RT rejection were dropped from analysis. Event-related brain potentials were also elicited from control subjects on two consecutive days. These data were used both to assess P300 test–retest reliability and to yield mean P300 values for comparison with patients.

### *Data Analysis*

**STATE ANALYSES.** We used both nonparametric and parametric approaches to test the hypothesized inverse relationship between each BPRS scale and each P300 amplitude measure over time. First, BPRS scores were regressed on P300 amplitudes for each patient, saving the slope of each patient’s regression line as the unit of analysis. Because these slopes were based on only a few data points (2–7), we initially analyzed them nonparametrically using one-tailed Wilcoxon signed-ranks tests (Siegel and Castellan 1988). Under the null hypothesis of no BPRS relationship with P300, the sum of the signed ranks of the slopes is zero. Under the directional alternative hypothesis, the sum of the ranks

Table 2. Intervals in Days between Event-Related Brain Potential Measurement Occasions for 36 Schizophrenic Patients

Patient	Number of days between successive measurements							Total number of occasions	Number of unmedicated occasions
	1	2	Measurement occasion				7		
			3	4	5	6			
1	0 <sup>c</sup>	14 <sup>c</sup>						2	0
2	0	14						2	2
3	0	42 <sup>c</sup>						2	1
4	0	14						2	2
5	0	13						2	2
6	0	43 <sup>c</sup>						2	1
7 <sup>a</sup>	0 <sup>c</sup>	14 <sup>c</sup>						2	0
8	0	8						2	2
9	0	14	28 <sup>c</sup>					3	2
10	0	12	15 <sup>c</sup>					3	2
11	0	14	28					3	3
12	0	7	28 <sup>c</sup>					3	2
13	0	4	31 <sup>c</sup>					3	2
14	0	6	28 <sup>c</sup>					3	2
15	0 <sup>c</sup>	13 <sup>c</sup>	28 <sup>c</sup>					3	0
16	0	14	28 <sup>c</sup>					3	2
17	0 <sup>c</sup>	14 <sup>c</sup>	28 <sup>c</sup>					3	0
18	0	13	28 <sup>c</sup>					3	2
19	0 <sup>c</sup>	337	45 <sup>c</sup>					3	1
20	0	8	27 <sup>c</sup>					3	2
21 <sup>b</sup>	0	7	1061					3	3
22	0	15	27 <sup>c</sup>					3	2
23	0	7	28 <sup>c</sup>					3	2
24	0	14	28 <sup>c</sup>					3	2
25	0	7	28 <sup>c</sup>					3	2
26	0 <sup>c</sup>	14 <sup>c</sup>	28 <sup>c</sup>					3	0
27	0 <sup>c</sup>	869	8	27 <sup>c</sup>				4	2
28	0 <sup>c</sup>	14 <sup>c</sup>	29 <sup>c</sup>	601				4	1
29	0	13	28 <sup>c</sup>	315	35			5	4
30	0	12	29 <sup>c</sup>	125	7			5	4
31	0	14	28 <sup>c</sup>	406	49			5	4
32	0	7	28 <sup>c</sup>	28	7			5	4
33	0	568	7	603	105	47 <sup>c</sup>		6	5
34	0	14 <sup>c</sup>	28 <sup>c</sup>	112	7	28 <sup>c</sup>		6	3
35	0	7	28 <sup>c</sup>	28	7	22		6	5
36	0 <sup>c</sup>	64	7	26 <sup>c</sup>	466	4	35	7	5

<sup>a</sup>Patient 7 measured only in automatic auditory paradigm.  
<sup>b</sup>Patient 21 measured only in effortful paradigms.  
<sup>c</sup>Event-related brain potential obtained while patient taking antipsychotic medication.

of negative slopes is significantly greater than the sum of the ranks of positive slopes, indicating a preponderance of negative slopes. This nonparametric approach diminishes the influence of outliers and addresses whether the predicted inverse relationship between BPRS and P300 is present in a significant majority of patients; however, it has limited power, does not take within- or between-subject variance into account, and does not estimate the overall slope across patients.

Accordingly, we also performed parametric multiple linear regression of BPRS scores on P300 amplitude, entering all patients and test occasions, to assess the covariation between BPRS and P300 within patients over time. The Patient effect was dummy coded (Pedhazur 1982) and entered into the regression analysis first, accounting for BPRS variation associated with interpatient differences. P300 amplitude was entered second, thereby using only within-patient P300 scores to predict within-

patient BPRS scores. Thus, only within-patient variation over test occasions contributed to the estimate of the BPRS-P300 relationship. The Patient × P300 interaction was entered third, testing between-patient differences in the slopes of the BPRS-P300 regression lines. A nonsignificant (two-tailed) interaction was dropped from the model, resulting in a common slope (i.e., the partial regression coefficient for P300) but different intercepts across patients. This common slope represented the average of all individual patient slopes, each weighted by the patient's P300 variance. If the Patient × P300 interaction was significant, indicating that patient slopes differed significantly, it was retained in the model and the resulting partial regression coefficient for P300 represented the unweighted average of all individual patient slopes. A one-tailed *t* test determined whether the partial regression coefficient (i.e., the average slope) for P300 amplitude was significantly less than zero.

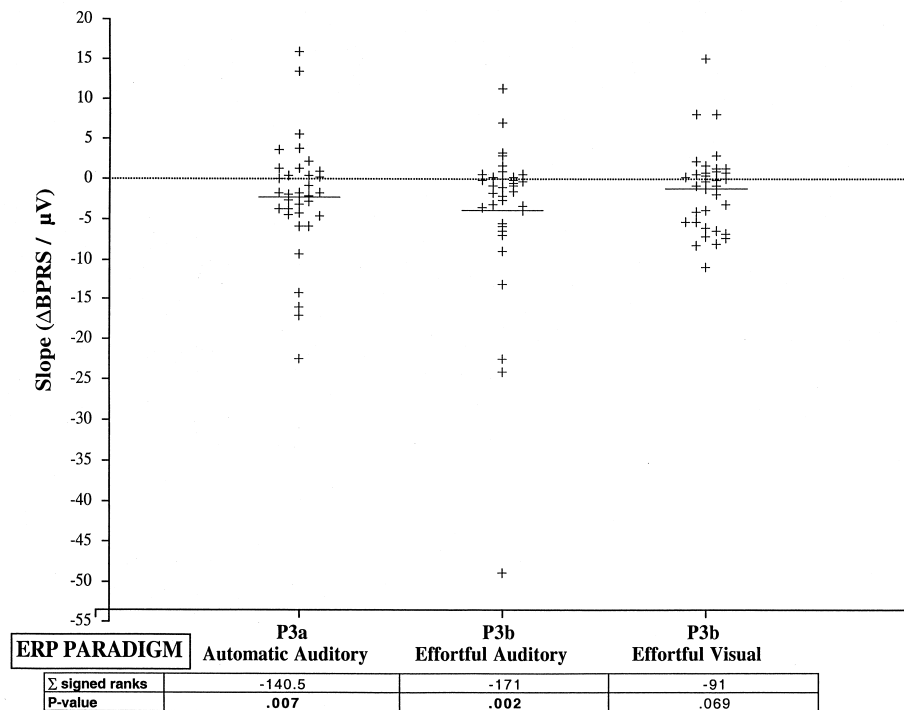


Figure 1. Patient slopes based on regression of Brief Psychiatric Rating Scale (BPRS) Total scores on P300 amplitudes for each patient. Crosses represent patient slopes estimated for each of the three event-related brain potential (ERP) paradigms used to elicit P300 amplitudes: automatic auditory, effortful auditory, and effortful visual. Solid lines indicate the mean slopes. Results of the one-tailed Wilcoxon signed-ranks tests are shown below each distribution. Note that a significant majority of the patients had negative slopes for the two auditory paradigms, with a nonsignificant trend for the visual paradigm. Negative slopes indicate that as BPRS scores increase, P300 amplitudes decrease.

To control for the potential confounding effects of medication status on clinical state and P300 amplitude, both the Wilcoxon tests and the multiple regression analyses were repeated using only those testing occasions on which patients were unmedicated. To remain in this analysis, each patient had to have at least two unmedicated measurement occasions.

In addition, P300 amplitudes associated with each patient's highest and lowest BPRS Total score were identified and compared in a two-way (Clinical State  $\times$  Paradigm) repeated measures ANOVA.

**TRAIT ANALYSES.** To assess trait characteristics of P300 in schizophrenia, P300 amplitudes associated with patients' best and worst clinical states were each compared with normal controls in two-way (Group  $\times$  Paradigm) repeated measures ANOVAs. Next, average P300 amplitude and BPRS scores were calculated for each patient over all testing occasions to capture enduring individual differences in P300 and symptomatology, and then these mean scores were correlated. In addition, intraclass correlations (ICC; Snedecor and Cochran 1989; Winer 1971) were calculated to evaluate the stability of P300 over testing occasions in patients, and are referred to as "stability coefficients." These were compared to P300 test-retest reliability coefficients, also ICCs (Cronbach et al 1972), calculated over two consecutive days from the first measurement occasion in patients and control subjects. The reliability coefficients were

adjusted using the Spearman-Brown Prophecy Formula because the final P300 measures were averages over two consecutive days for each measurement occasion (Anastasi 1982). The reliability coefficients set upper limits on the stability coefficients because P300 could be no more stable than its test-retest reliability. We expected the stability coefficients to be smaller than the reliability coefficients in patients, which in turn were expected to be smaller than the reliability coefficients in control subjects. Reductions in patient reliability and stability coefficients relative to control subject reliability coefficients were presumed to result from clinical state fluctuations. For all statistical tests,  $\alpha = .05$ .

## Results

### State Analyses

Wilcoxon signed-ranks tests of the individual patient slopes, estimated from regression of BPRS Total scores on P300 amplitudes for each patient, indicated a significant number of negative slopes for the two auditory ERP paradigms and a nonsignificant trend ( $p < .07$ ) for the visual paradigm, all showing smaller P300 amplitudes associated with higher BPRS Total scores within patients over time (see Figure 1). For all three ERP paradigms, the sums of the signed ranks

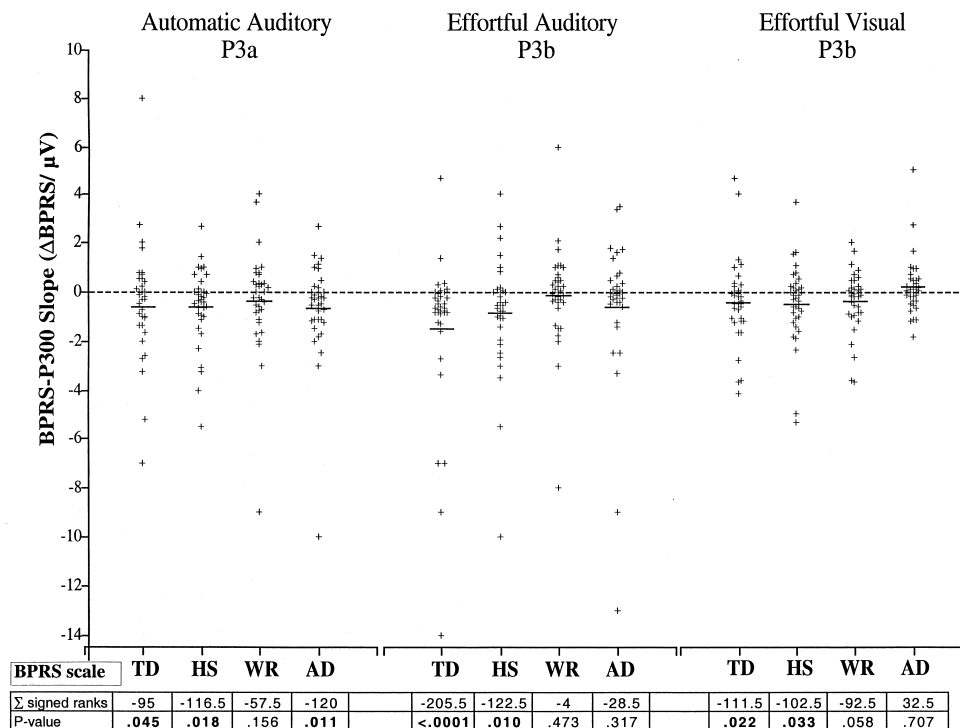


Figure 2. Patient slopes based on regression of Brief Psychiatric Rating Scale (BPRS) subscales on P300 amplitudes elicited in automatic auditory, effortful auditory, and effortful visual paradigms. Crosses represent patient slopes, and solid lines indicate the mean slopes. Results of one-tailed Wilcoxon signed-ranks tests are shown below each distribution. Note that a significant majority of the patients had negative slopes for Thinking Disturbance and Hostility-Suspiciousness across the three P300 paradigms. In addition, a trend was observed showing a preponderance of negative slopes for Withdrawal-Retardation in the effortful visual paradigm. TD, Thinking Disturbance; HS, Hostility-Suspiciousness; WR, Withdrawal-Retardation; AD, Anxiety-Depression.

were significantly negative for BPRS Thinking Disturbance and Hostility-Suspiciousness, with an additional significant effect for Anxiety-Depression with P3a in the automatic auditory paradigm and a nonsignificant trend ( $p = .058$ ) for Withdrawal-Retardation with P3b in the effortful visual paradigm (see Figure 2).

Multiple regression analyses largely corroborated these nonparametric analyses (see Table 3). Except in the regression model predicting Hostility-Suspiciousness from effortful visual P3b, the Patient  $\times$  P300 amplitude interactions were dropped due to nonsignificance, suggesting homogeneous slopes across patients. Controlling for Patient effects, automatic P3a amplitude significantly predicted BPRS Total, Thinking Disturbance, Hostility-Suspiciousness, and Anxiety-Depression, consistent with the corresponding Wilcoxon tests. Effortful auditory P3b significantly predicted BPRS Total, Thinking Disturbance, and Hostility-Suspiciousness, consistent with the Wilcoxon tests, but also significantly predicted Withdrawal-Retardation. Effortful visual P3b significantly predicted BPRS Total, Thinking Disturbance, Hostility-Suspiciousness, and Withdrawal-Retardation, consistent with the Wilcoxon tests.

When the above analyses were repeated using only

occasions on which patients were unmedicated (28 patients, 71 occasions), only two significant relationships persisted using the Wilcoxon tests: effortful auditory P3b with BPRS Total ( $\Sigma$  signed ranks =  $-62$ ,  $p = .03$ ) and Thinking Disturbance ( $\Sigma$  signed ranks =  $-80.5$ ,  $p = .0008$ ). The multiple regression analyses corroborated these results (Table 3). Furthermore, in the regression analyses, automatic auditory P3a persisted in significantly predicting BPRS Total and Anxiety-Depression, with the Wilcoxon test showing a trend for Anxiety-Depression ( $\Sigma$  signed ranks =  $-39.5$ ,  $p = .085$ ). No significant relationships emerged in the unmedicated sample between BPRS scores and effortful visual P3b. Whenever the P300 effect was significant or showed a trend, P300 amplitude decreased as clinical severity increased.

To further assess clinical state effects, P300 amplitudes associated with each patient's best and worst BPRS Total score were identified (mean low score =  $40 \pm 6.6$ ; mean high score =  $52 \pm 7.4$ ; paired  $t$  test =  $8.7$ ,  $p < .0001$ ). A two-way (Clinical State  $\times$  ERP Paradigm) repeated measures ANOVA showed significant effects for Clinical State [best P300 > worst P300;  $F(1,33) = 4.59$ ,  $p = .02$ , one-tailed], Paradigm [visual P3b > auditory P3b > auditory

Table 3. Hierarchical Multiple Regression of Brief Psychiatric Rating Scale (BPRS) on P300 Amplitude in Schizophrenic Patients

BPRS dependent variable	Predictor	Step entered	Full sample ( $n = 36$ ) <sup>a</sup>		Unmedicated sample ( $n = 28$ ) <sup>b</sup>	
			R <sup>2</sup>	b coefficient <sup>c</sup>	R <sup>2</sup>	b coefficient <sup>c</sup>
<i>Automatic Auditory P3A</i>						
Total	Patient	1	.458		.570	
	P300 Amplitude	2	.517	-1.72 <sup>f</sup>	.616	-1.58 <sup>d</sup>
Thinking Disturbance	Patient	1	.583		.670	
	P300 Amplitude	2	.600	-0.34 <sup>d</sup>	.674	-0.18
Hostility-Suspiciousness	Patient	1	.604		.634	
	P300 Amplitude	2	.626	-0.38 <sup>d</sup>	.642	-0.24
Withdrawal-Retardation	Patient	1	.550		.701	
	P300 Amplitude	2	.556	-0.16	.705	-0.14
Anxiety-Depression	Patient	1	.527		.580	
	P300 Amplitude	2	.567	-0.36 <sup>e</sup>	.635	-0.44 <sup>e</sup>
<i>Effortful Auditory P3B</i>						
Total	Patient	1	.477		.586	
	P300 Amplitude	2	.549	-1.45 <sup>f</sup>	.618	-1.05 <sup>d</sup>
Thinking Disturbance	Patient	1	.607		.686	
	P300 Amplitude	2	.672	-0.51 <sup>g</sup>	.723	-0.45 <sup>e</sup>
Hostility-Suspiciousness	Patient	1	.616		.634	
	P300 Amplitude	2	.657	-0.37 <sup>f</sup>	.647	-0.24
Withdrawal-Retardation	Patient	1	.556		.705	
	P300 Amplitude	2	.573	-0.20 <sup>d</sup>	.710	-0.12
Anxiety-Depression	Patient	1	.515		.578	
	P300 Amplitude	2	.520	-0.10	.584	-0.12
<i>Effortful Visual P3B</i>						
Total	Patient	1	.487		.586	
	P300 Amplitude	2	.525	-1.03 <sup>e</sup>	.602	-0.66
Thinking Disturbance	Patient	1	.609		.686	
	P300 Amplitude	2	.634	-0.31 <sup>e</sup>	.693	-0.17
Hostility-Suspiciousness	Patient	1	.607		.634	
	P300 Amplitude	2	.626	-0.25 <sup>d</sup>	.649	-0.23
	Patient × P300	3	.839	-0.48 <sup>d</sup>	.899	-0.54
Withdrawal-Retardation	Patient	1	.556		.705	
	P300 Amplitude	2	.570	-0.18 <sup>d</sup>	.709	-0.09
Anxiety-Depression	Patient	1	.512		.578	
	P300 Amplitude	2	.516	-0.08	.582	-0.09

<sup>a</sup>Thirty-six patients measured on multiple occasions, irrespective of medication status, for total of 120 observations.

<sup>b</sup>Twenty-eight patients measured on multiple occasions, all unmedicated, for total of 71 observations.

<sup>c</sup>Partial regression coefficient for P300, indicating the slope of the regression line averaged over patients.

<sup>d</sup> $p \leq .05$ . <sup>e</sup> $p \leq .01$ . <sup>f</sup> $p \leq .001$ . <sup>g</sup> $p \leq .0001$  (one-tailed).

P3a;  $F(2,66) = 48.40$ ,  $p < .0001$ ], but no Clinical State × Paradigm interaction [ $F(2,66) = 0.06$ ,  $p = .94$ ]. As shown by the grand average ERP wave forms (Figure 3), P300 amplitudes tended to be smaller when patients were in their worst compared with their best clinical states.

### Trait Analyses

Comparison of P300 amplitudes from patients in their best clinical states with those from healthy control subjects

(Figure 3) revealed significant effects for Group [ $F(1,63) = 2.65$ ,  $p = .054$ , one-tailed], Paradigm [ $F(2,126) = 57.49$ ,  $p < .0001$ ], and the Group × Paradigm interaction [ $F(2,126) = 3.12$ ,  $p = .024$ ]. Follow-up  $t$  tests showed that patients had reduced P300 amplitudes for the two auditory paradigms (automatic P3a:  $t[66] = 1.81$ ,  $p = .04$ ; effortful P3b:  $t[66] = 2.09$ ,  $p = .02$ ; both one-tailed), but not for the visual paradigm ( $t[66] = -0.11$ ,  $p = .54$ , one-tailed). The same pattern of group differences across paradigms, but with stronger

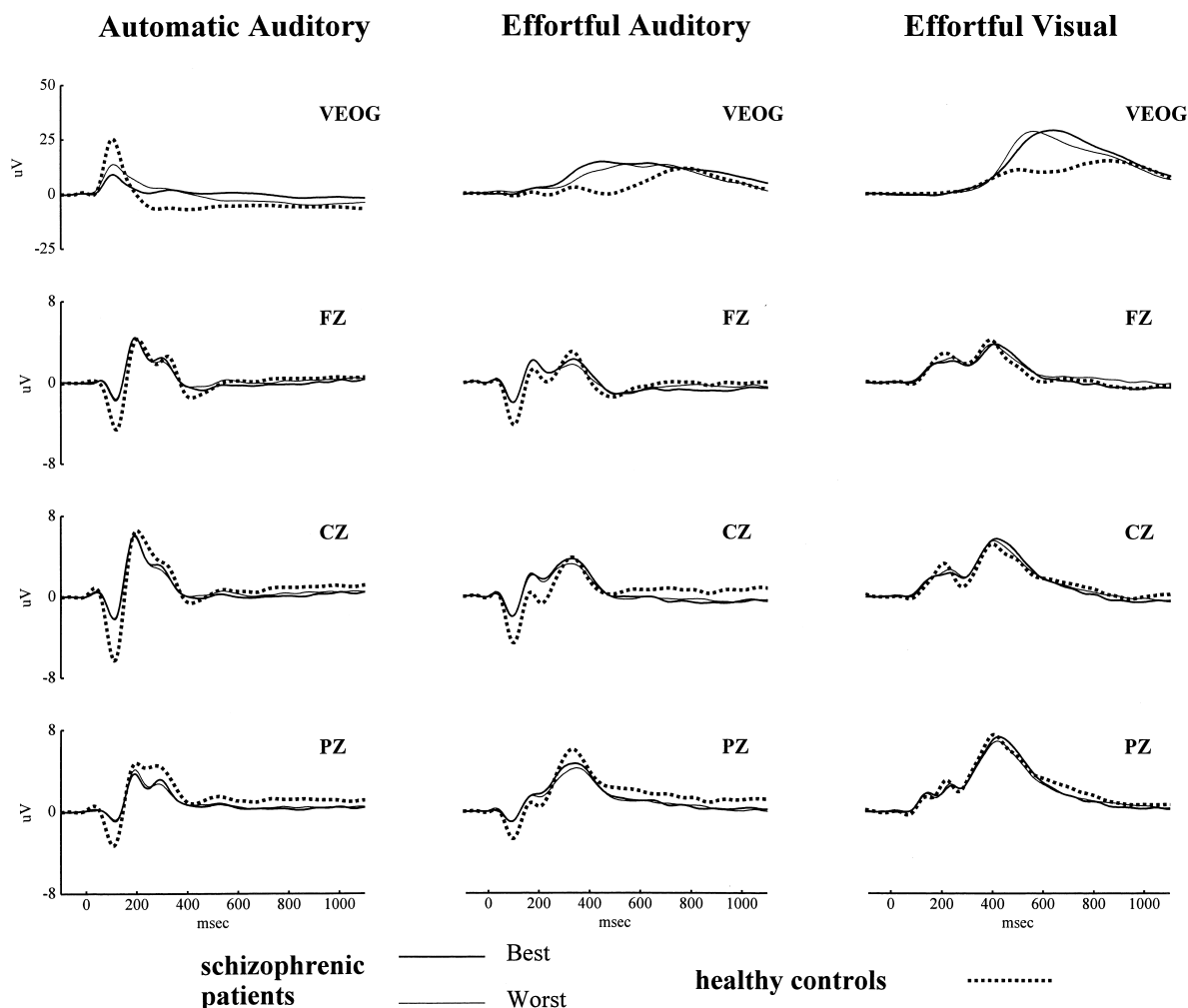


Figure 3. Average event-related brain potential (ERP) wave forms from schizophrenic patients in their best and worst clinical states (based on Brief Psychiatric Rating Scale [BPRS] Total scores), as well as from healthy control subjects. Mean  $\pm$  SD BPRS Total scores for best clinical state =  $40 \pm 6.6$ , and for worst clinical state =  $52 \pm 7.4$ . Note that even when in their best clinical state, P300 amplitudes in schizophrenic patients tend to be smaller than in control subjects across both auditory ERP paradigms.

effects, emerged when the P300s from patients in their worst clinical states were considered. Thus, even when they were least symptomatic, patients continued to exhibit auditory P300 amplitude reductions relative to control subjects.

Patient P300 amplitude and BPRS scores averaged over all test occasions were correlated to address associations between stable aspects of P300 and enduring clinical symptoms. Higher BPRS Withdrawal-Retardation was significantly associated with smaller P3b amplitudes (effortful auditory:  $r = -.40$ ,  $p = .008$ ; visual:  $r = -.31$ ,  $p = .035$ ; both one-tailed). In addition, an unexpected positive relationship emerged between higher BPRS Hostility-Suspiciousness and larger visual P3b amplitudes ( $r = .34$ ,  $p = .05$ , two-tailed).

P300 stability coefficients for patients, and test-retest

reliability coefficients for both patients and control subjects, are presented in Table 4. Reliabilities across ERP paradigms ranged from .84 to .93 in control subjects and .82 to .87 in patients. Stability coefficients were consistently smaller than their corresponding reliability coefficients. Nonetheless, P300 amplitudes in schizophrenic patients showed moderate stability over time, suggesting that there is more variability between patients than within patients. That is, when P300 is assessed in patients repeatedly over time, a relatively large percentage of its variance is attributable to individual differences between patients (66–72% trait variance, indicated by stability coefficients), a relatively small percentage of its variance is attributable to test-retest unreliability (7–16% measurement error variance, indicated by reliability coefficients in normal control subjects), and the balance of its variance is

Table 4. Reliability and Stability Coefficients for P300 Amplitudes

ERP paradigm	Intraclass correlation coefficients		
	Healthy control subjects ( <i>n</i> = 33) test–retest reliability	Schizophrenic patients ( <i>n</i> = 35) test–retest reliability	Schizophrenic patients ( <i>n</i> = 35) stability
Automatic auditory P3a	.84	.82	.68
Effortful auditory P3b	.93	.82	.66
Effortful visual P3b	.86	.87	.72

Test–retest reliability coefficients are intraclass correlations of repeated event-related brain potential (ERP) testing on two consecutive days, and have been adjusted based on the Spearman–Brown Prophecy Formula. Stability coefficients are based on multiple ERP measurement occasions, ranging from 2 to 7, with each occasion representing the average of the day 1 and day 2 P300 amplitudes.

attributable to state variation associated with schizophrenia (14–27% state variance, inferred by subtracting trait and measurement error variance from 100%). This parsing of the P300 variance is summarized in Table 5.

To further elucidate the similarities and differences between the three P300 measures, their inter-correlations were calculated for all patients and measurement occasions (*N* = 121). P3b amplitudes from the auditory and visual effortful paradigms were strongly interrelated ( $r = .76$ ,  $p \leq .0001$ ) but were only modestly related to automatically elicited P3a amplitude (with auditory P3b,  $r = .30$ ,  $p = .0009$ ; with visual P3b,  $r = .20$ ,  $p = .03$ ).

### Performance Analyses

The correlations between performance and P3b measures from all patients and measurement occasions (*N* = 121) were significant (auditory P3b vs. RT,  $r = -.36$ ,  $p = .0001$ ; auditory P3b vs. errors,  $r = -.34$ ,  $p = .0002$ ; visual P3b vs. RT,  $r = -.37$ ,  $p = .0001$ ; visual P3b vs. errors,  $r = -.24$ ,  $p = .008$ ), suggesting that faster RTs and fewer errors were associated with larger P3b amplitudes. However, performance measures from both paradigms failed to track clinical state fluctuations in multiple regression analyses similar to those conducted for P300. Moreover, the average performance measures across all measurement occasions did not significantly correlate with

any of the average BPRS measures, indicating that task performance was unrelated to clinical severity.

### Discussion

In this retrospective longitudinal study, three types of P300 (auditory and visual effortful P3b, auditory automatic P3a) were recorded repeatedly over the course of hospitalization and treatment for schizophrenia. Auditory P3a and P3b were reduced in amplitude in schizophrenic patients relative to normal control subjects, even when patients were least symptomatic, consistent with their roles as trait markers of schizophrenia. In addition, amplitudes of all three types of P300 tracked global changes in clinical state and selective changes in the BPRS symptom complexes, decreasing as symptoms worsened and increasing as symptoms improved, suggesting that they can also serve as clinical state markers in schizophrenia. These results are consistent with prior longitudinal studies showing that treatment with antipsychotic medications are associated with increases in auditory P300 amplitudes (Asato et al 1996; Coburn et al 1998; Hirayasu and Ogura 1996; Maeda et al 1996; Schall et al 1998; Umbricht et al 1998), further corroborate reports of correlations between increases in auditory P300 amplitude and the degree of clinical improvements in positive (Schall et al 1998; Turetsky et al 1998) or negative symptoms (Turetsky et al 1998), but are only partially consistent with a prior study (Duncan et al 1987) showing that visual but not auditory P300 amplitudes increase with clinical improvement.

To control for medication effects as a possible confounding variable for the association between P300 amplitude and clinical severity, we performed analyses of measurements obtained when patients were either unmedicated or receiving a placebo. Independent of medication effects, only auditory P300 amplitudes persisted in tracking fluctuations in global clinical severity, with additional tracking of positive symptoms by P3b and anxiety-depression symptoms by P3a; however, reduced power in these subanalyses may have limited their sensitivity to the other state effects observed in the full sample. Furthermore, it is

Table 5. Percentage of P300 Variance Due to Trait, State, and Measurement Error in Schizophrenic Patients Assessed Repeatedly Over Time

ERP paradigm	Trait variance	State variance	Test–Retest error variance
Automatic auditory P3a	68%	16%	16%
Effortful auditory P3b	66%	27%	7%
Effortful visual P3b	72%	14%	14%

Trait variance estimates are based on the patient stability coefficients over time. Test–retest error variance estimates are calculated as 100% minus the reliability coefficients derived from healthy controls. State variance estimates are calculated as 100% – (% trait variance + % error variance). ERP, event-related brain potential.

possible that the visual P300 is more sensitive to clinical improvements produced by medication than to clinical fluctuations that constitute the “natural history” of schizophrenia, consistent with Duncan and colleagues’ report (Duncan et al 1987) that only the treatment responders showed the increase in visual P3b amplitudes after starting antipsychotic medication.

The fact that P300 amplitude tracked overall severity and positive symptoms suggests that psychosis interferes with fundamental information-processing functions involved both in automatic orienting to salient stimuli and effortful attention to target stimuli. Possibly, preoccupation with hallucinations, delusions, and paranoia utilizes neural resources that would otherwise be available for processing environmental stimuli. Similarly, thought disorganization may be associated with reduced efficiency or fidelity of neural circuitry that is normally involved in regulating attention to salient or relevant features of the environment.

Moreover, tracking of positive symptoms by P300 amplitude may reflect disruption of neuroanatomical structures common to both psychosis and P300 generation. Depth electrode recordings have localized the neural generators of the P3a system for orienting attention to the anterior cingulate, dorsolateral prefrontal, and inferior parietal cortices, and the generators of the P3b system for encoding cognitively relevant events to the hippocampus, superior temporal sulcus, lateral orbitofrontal cortex, and intraparietal sulcus (Halgren et al 1998). Structural and functional abnormalities of many of these brain regions have been found in schizophrenia, including prefrontal cortex (e.g., Liddle et al 1992; Schlaepfer et al 1994; Weinberger et al 1986), anterior cingulate (e.g., Benes 1993; Carter et al 1997; Liddle et al 1992), hippocampus (for review, see Nelson et al 1998), and superior temporal gyrus (e.g., Barta et al 1990; Schlaepfer et al 1994; Shenton et al 1992), and these abnormalities have been shown to correlate with clinical symptoms (e.g., Barta et al 1990; Liddle et al 1992; Shenton et al 1992).

The relatively weak relationships of effortfully elicited P3b amplitudes with negative symptoms in the full sample may reflect the fact that negative symptoms show little variability over time (Johnstone et al 1986; Mathalon and Pfefferbaum 1997; Mueser et al 1991; Pfohl and Winokur 1982; Pogue-Geile and Harrow 1985; Putnam et al 1996). Nonetheless, our finding that P3b, but not P3a, amplitudes tracked negative symptoms are consistent with a prior study (Turetsky et al 1998) showing that the left temporal P300, largely reflecting P3b, but not the frontal P300, largely reflecting P3a, increased in amplitude with improvement in negative symptoms. This suggests that the motivational deficits associated with negative symptoms selectively reduce the effortfully elicited P3b, perhaps

because motivational factors affect attention to task-relevant stimuli but do not affect the orienting response during automatic elicitation of P3a. In contrast, the sensitivity of P3a, but not P3b, amplitudes to fluctuations in depression-anxiety symptoms suggests that dysphoric mood states may dampen orienting responses to salient stimuli without disrupting effortfully directed attention to target stimuli. However, some (e.g., Pholien et al 1987; Roth et al 1981; Urcelay-Zaldua et al 1995), but not all (e.g., Gangadhar et al 1993; Sara et al 1994), studies show smaller effortful auditory P3b amplitudes in clinically depressed patients, indicating that effortful attention may also be disrupted by dysphoric mood.

In addition to clinical state effects, the present study demonstrated trait-like reductions of auditory, but not visual, P300 amplitudes in schizophrenia, confirming other reports (e.g., Duncan et al 1987; Pfefferbaum et al 1989). Indeed, even when the schizophrenic patients were most symptomatic, visual P3b amplitude was not reduced. Sparing of visual attentional processes in schizophrenia, relative to auditory processing, supports the view that schizophrenia preferentially alters auditory-based brain functions (Andreasen 1997). Yet, our results indicate that even though visual P3b amplitudes appear intact in schizophrenia, they may still be affected by clinical symptom fluctuations (see also Duncan et al 1987). In contrast, auditory P3a and P3b amplitudes were significantly reduced, even when these inpatients were in their best, albeit still moderately symptomatic, clinical state. Others have reported that even clinically stabilized outpatients exhibit residual symptoms and auditory P300 amplitude reduction (Juckel et al 1996; Michie et al 1990; Rao et al 1995).

P300 amplitude showed moderate stability in patients over time, despite its sensitivity to clinical state, suggesting greater variability between patients than within patients and further supporting trait-dependent aspects of P300. However, P300 stability coefficients in the patients were smaller than their corresponding test-retest reliability coefficients, indicating that state-dependent influences reduce the long-term stability of P300. Furthermore, auditory P300 reliability coefficients were lower in patients than control subjects, perhaps reflecting greater daily P300 amplitude variability or decreased signal-to-noise ratios in schizophrenia. Thus, whereas a core psychophysiological feature of the “trait” of schizophrenia is a small auditory P300 amplitude, this abnormality is not just a static marker of the underlying disease or its genotype but is influenced by ongoing changes in the patient’s clinical state.

Additional trait effects emerged in our correlational analyses of each patient’s mean BPRS and P300 scores averaged over all measurement occasions. Mean scores tap more enduring individual differences in symptom profiles and P300 amplitudes, characterizing trait-like aspects of

each patient's illness course. Patients with more negative symptoms over time, perhaps reflecting the deficit syndrome in schizophrenia (Carpenter et al 1993), had smaller auditory and visual P3b amplitudes. The fact that auditory and visual P3b amplitudes tended to show similar relationships with clinical variables is not surprising in light of their relatively strong intercorrelation. Likewise, the dissociation of P3b and P3a amplitudes in terms of their relationships with clinical variables is consistent with their relatively small intercorrelations.

Cross-sectional studies have demonstrated associations of both positive symptoms (e.g., Egan et al 1994; Juckel et al 1996; Laurent et al 1993; Levit et al 1973; McCarley et al 1991; Roth et al 1981; Ward et al 1991) and negative symptoms (Blackwood et al 1987; Eikmeier et al 1992; Maurer et al 1990; Pfefferbaum et al 1989; Strik et al 1993; Ward et al 1991) with reduced auditory P300 amplitude in schizophrenia. The results of our longitudinal analyses are consistent with these cross-sectional studies and also extend them by showing that reduced P300 reflects both trait and state aspects of the pathophysiology of schizophrenia. Because patients differ from each other in their absolute P300 amplitudes and fluctuate around their own characteristic amplitudes with clinical state (Figure 4), longitudinal repeated measure studies are essential for disentangling state and trait influences and for detecting clinical relationships.

Many prior longitudinal studies of auditory P300 amplitude and clinical symptoms have been treatment studies (Asato et al 1996; Blackwood et al 1987; Coburn et al 1998; Ford et al 1994c; Hirayasu and Ogura 1996; Schall et al 1998; Umbricht et al 1998). Whereas some of these studies have shown auditory P300 amplitudes to increase with typical (Asato et al 1996; Coburn et al 1998; Hirayasu and Ogura 1996) or atypical (Schall et al 1998; Umbricht et al 1998) antipsychotic medication, most either did not find (Coburn et al 1998; Umbricht et al 1998) or did not report (Asato et al 1996; Blackwood et al 1987; Hirayasu and Ogura 1996) correlations between changes in P300 amplitude and clinical state. In the absence of such correlations, findings of P300 amplitude increases with antipsychotic treatment raise the possibility of direct medication effects independent of clinical improvement. However, limited variance in change scores across subjects undergoing effective treatment could account for failures to find correlations between P300 change and symptom change.

Two features of our study may have facilitated detection of P300–clinical state relationships. First, clinical and P300 data were obtained over multiple test occasions encompassing both clinical drug trials and the naturalistic course of repeated hospitalizations, increasing the within-subject variance available for detection of correlations

between P300 amplitude and clinical state. The within-subject statistical approach taken in the present study using each individual's BPRS-P300 slope as the unit of analysis not only avoided the problem of limited change score variance across patients but also made use of all available measurement occasions for each patient. Second, by averaging the P300 measurements obtained on two consecutive days, their test–retest reliabilities were increased (Anastasi 1982), thereby increasing their sensitivity to clinical state and trait effects.

The present study also suffered from several limitations. This was not a prospectively designed longitudinal study, so the number of measurement occasions and the time intervals between occasions varied across subjects. Moreover, measurement occasions were not randomly sampled from the patients' illness course, but rather were mostly dictated by drug treatment protocols. Medication status was not systematically controlled nor varied, limiting our ability to address the role of medication in mediating BPRS-P300 relationships. In addition, patients in the study were hospitalized on all measurement occasions, perhaps restricting the range of clinical severity represented in the sample and decreasing the generalizability of the results. Thus, the results of this study require some caution in interpretation, pending replication of these relationships in prospectively designed multiple observation longitudinal studies.

Schizophrenia is a disorder with significant clinical heterogeneity in symptom domains (Buchanan and Carpenter 1994; Liddle 1987) and longitudinal course (Arndt et al 1995; Ciompi 1980; Mithalon and Pfefferbaum 1997). Whether schizophrenia is a progressive or nonprogressive disease, and whether there are distinct clinical subsyndromes with distinguishable symptoms and courses, are among the empirical questions that remain unsettled. Resolution of these questions will require moving beyond clinical symptoms to their underlying biological substrates. Simple cross-sectional comparisons of schizophrenic individuals and healthy control subjects have limited potential to elucidate the underlying pathophysiology and clinical heterogeneity of schizophrenia. Biological abnormalities detected by cross-sectional investigations, such as the often replicated reduction of P300 amplitude in schizophrenia (Ford et al 1992), reflect both static and dynamic pathophysiologic processes. Static processes include genetic vulnerability to the illness or stable features of the schizophrenia phenotype that reflect abnormal brain development and/or subtle structural brain lesions. Dynamic processes include progressive aspects of the disease, both neurodevelopmental and neurodegenerative, as well as nonprogressive fluctuations in specific symptom domains over time. Because of this dynamic aspect of the disease, biological and clinical data must be

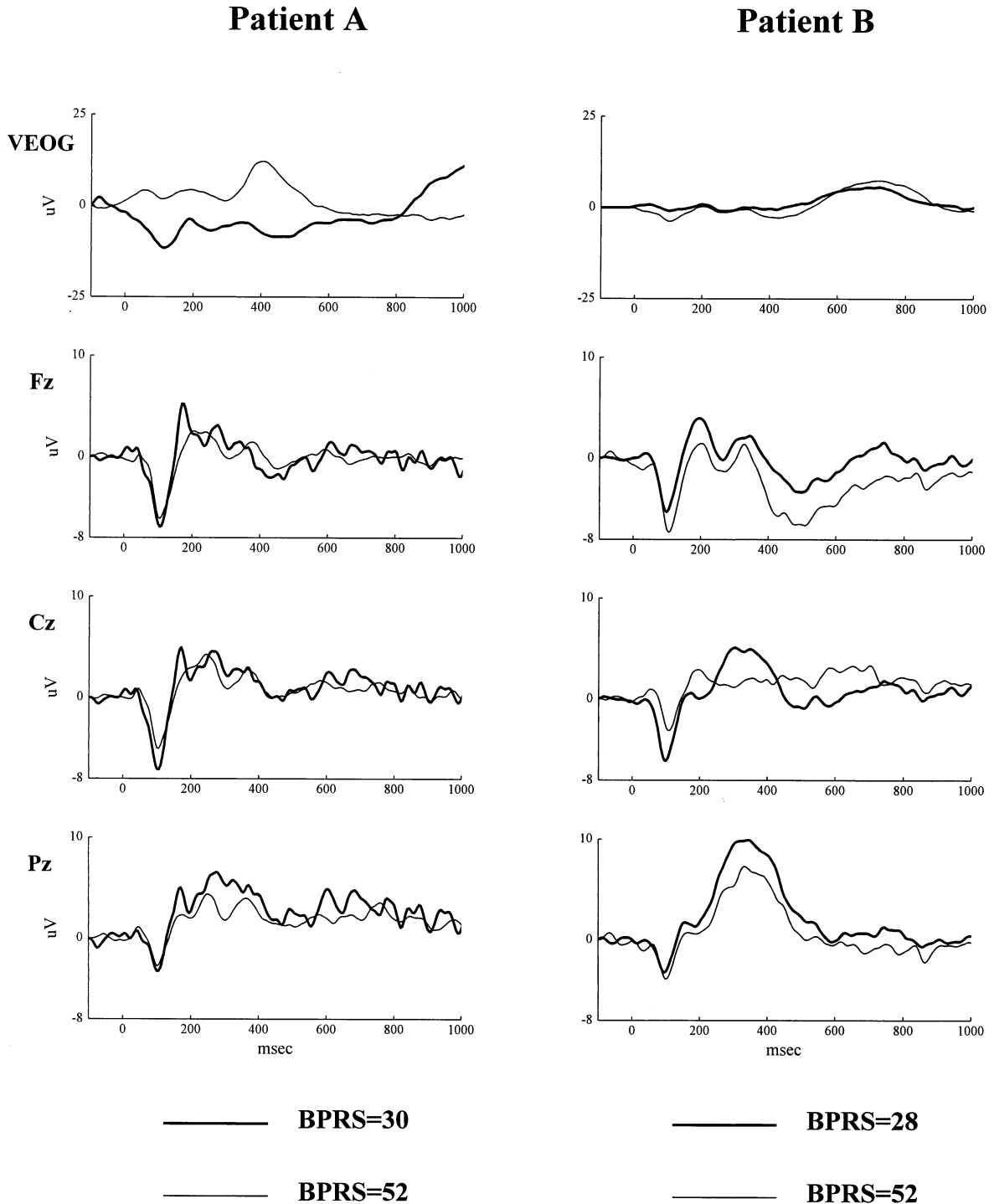


Figure 4. Effortful auditory event-related brain potential data for two patients with schizophrenia whose total Brief Psychiatric Rating Scale (BPRS) scores changed considerably over two time points. Darker lines depict wave forms obtained when BPRS scores were lower, and lighter lines depict wave forms obtained when BPRS scores were higher (more severe clinical state). Note that P300 amplitude is smaller when patients are more symptomatic, even though Patient A at his best clinical state (BPRS Total = 30) has a smaller P300 amplitude than Patient B at his worst clinical state (BPRS Total = 52). Depending on the representation of such patients in a cross-sectional sample and their particular clinical states when assessed, simple correlations between P300 amplitude and clinical ratings may be positive, negative, or nonexistent. This underscores the importance of repeated measurements for detecting state effects.

collected from patients at various times over the clinical course. Moreover, we must be prepared for the possibility that a biological abnormality may reflect both static and dynamic aspects of the disease process. Such is the case for auditory P300 amplitude reduction in schizophrenia, which was shown both to vary with clinical state and yet to remain consistently reduced in schizophrenic patients relative to healthy control subjects.

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