

# Impaired P3 Generation Reflects High-Level and Progressive Neurocognitive Dysfunction in Schizophrenia

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**Background:** In this study, we assessed the integrity of several components of the event-related potential (ERP) associated with different levels of visual and auditory processing in patients with schizophrenia. The objective was to clarify whether high-level attention-dependent cognitive deficits, as indexed by the P3 component, in patients with schizophrenia are related to or originate from potential preceding deficits at lower levels of information processing, as indexed by earlier-occurring ERP components. Also, given that the auditory P3 amplitude has recently been observed to be inversely correlated with illness duration and, hence, may potentially track the operation of a putative neurodegenerative process across the illness course, we recruited patients with schizophrenia varying greatly in illness duration to attempt to replicate this observation.

**Methods:** Multichannel ERPs were recorded in 22 patients with schizophrenia at different stages of illness and 22 age-matched healthy control subjects while they performed a visual and auditory oddball task.

**Results:** Patients displayed smaller P3 amplitudes to visual novel and auditory target stimuli than did control

subjects, whereas small or no significant between-group differences were observed in sensory-evoked and cognitive-related ERP components preceding P3. Additionally, patients showed a distinct left-smaller-than-right auditory P3 temporal scalp voltage asymmetry. Furthermore, we replicated previous study results of an inverse correlation between the auditory P3 amplitude and illness duration.

**Conclusions:** These results indicate that high-level attention-dependent cognitive deficits central to schizophrenia do not originate from potential preceding impairments at lower levels of sensory, perceptual, or cognitive processing. The data support the view that schizophrenia is characterized by fundamental deficits in integrative cortical functions that specifically impair the ability to analyze and represent stimulus context to guide behavior. Moreover, abnormalities of the auditory P3 amplitude in schizophrenia seem to reflect a basic underlying pathophysiological process that is present at illness onset and progresses across the illness course.

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ONE OF THE MOST ROBUST biological abnormalities observed in schizophrenia is a smaller amplitude of the P3 (or P300) component of the event-related potential (ERP) elicited by using an auditory oddball paradigm in which a subject detects infrequent task-relevant (target) stimuli randomly presented among frequent, standard stimuli.<sup>1-15</sup> Because P3 reflects stimulus context and stimulus meaning,<sup>16-18</sup> the observed P3 reductions in schizophrenia support the view that dysfunction of attention and working memory represents a core cognitive deficit in this disorder.<sup>19-23</sup> Several researchers have also observed a prolonged P3 latency in schizophrenia,<sup>1,3,5,8,9</sup> but the interpretation of this finding has been

complicated by potential confounds of medication.<sup>5,9</sup>

An intriguing finding is that the auditory P3 is often selectively or more severely impaired relative to the visual P3 in schizophrenia.<sup>4,5,7,13</sup> Also, as opposed to the visual P3, the auditory P3 seems relatively independent of medication status<sup>3,5,7</sup> and clinical symptoms.<sup>3,4,7</sup> Such observations have led to the view that the visual P3 may serve as a state marker, reflecting the patient's current clinical status, whereas the auditory P3 may indicate, at least in part, a vulnerability or trait marker, reflecting an enduring, potentially genetically transmitted causative pathophysiological factor or process in schizophrenia.<sup>4,7,13</sup>

Another interesting observation is that patients with schizophrenia often show, in

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**Table 1. Demographic and Clinical Sample Characteristics\***

Characteristic	Patients (n = 22)	Control Subjects (n = 22)
Age, y	27.6 ± 9.5 (18-51)	27.7 ± 10.8 (18-57)
Sex, No. (%) F	5 (23)	7 (32)
Right-handedness, No. (%)	17 (77)	21 (96)
Race, No. (%) white	18 (82)	19 (86)
Education, y	13.0 ± 2.1 (8-16)†	15.3 ± 2.3 (12-19)
Age at illness onset, y	21.7 ± 5.2 (13-35)‡	NA
Illness duration, y	5.9 ± 7.0 (0.2-22.0)‡	NA
Antipsychotic medication dose, mg/d (CPZ equivalent)	462 ± 305 (60-1250)§	NA
Positive and Negative Syndrome Scale§		
Positive subscale, total score	12.0 ± 3.6 (7-21)	NA
Negative subscale, total score	14.4 ± 6.8 (7-29)	NA
General subscale, total score	27.0 ± 9.1 (16-54)	NA

Abbreviations: CPZ, chlorpromazine; NA, not applicable.

\*Data are given as mean ± SD (range) except where indicated otherwise.

†Patient and control means differ significantly at  $P < .01$  (2-tailed) by an independent-samples  $t$  test.

‡Includes 20 patients.

§Includes 19 patients.

addition to reductions across the midline, a localized left-smaller-than-right auditory P3 temporal scalp asymmetry, whereas healthy control subjects or patients with psychotic affective disorder do not show this P3 asymmetry.<sup>6,15,24-28</sup> Accordingly, the auditory P3 temporal lobe asymmetry may be specific to schizophrenia and has been linked, by using magnetic resonance imaging, to reduced gray matter volume of the left posterior superior temporal gyrus and left planum temporale.<sup>6,27</sup>

Recent studies have indicated that patients with schizophrenia may also exhibit deficits in visual and auditory ERP components that precede P3. These deficits include abnormalities of both relatively early, sensory-evoked components, such as P1,<sup>29</sup> N1,<sup>5,8,25,30,31</sup> and P2<sup>5,25,30</sup> and late cognitive-related components, such as N2<sup>8,25,31</sup> and mismatch negativity (MMN).<sup>31-36</sup> These deficits, however, do not appear to be as robust as P3 reduction, often varying as a function of stimulus and task parameters (eg, physical and temporal stimulus properties)<sup>31,34,35</sup> and subject sample characteristics (eg, recent-onset vs chronic schizophrenia).<sup>3,36</sup> Notwithstanding, these results raise the possibility that schizophrenia is associated with deficits not only at a high (cognitive, semantic) level of information processing, as reflected in P3 reduction, but also at lower (sensory, perceptual) processing levels, as evidenced by deficits in earlier-occurring components. To address this issue, we assessed the integrity of several ERP components related to different levels of visual and auditory processing in patients with schizophrenia.

The present study was aimed at clarifying whether high-level attention-dependent cognitive deficits, as in-

dexed by P3, in patients with schizophrenia are related to, or perhaps even originate from, potential preceding deficits at lower levels of information processing, as indexed by earlier-occurring ERP components. On the basis of previous ERP study results, as reviewed earlier, and the theoretical conceptualization that the pathology of schizophrenia involves multifocal diffuse abnormalities of brain function and structure,<sup>22,23,37-39</sup> rather than a single or specific localized abnormality, we hypothesized that patients with schizophrenia would probably display widespread independent deficits at both relatively low and high levels of processing in both the visual and auditory modalities. Additionally, given that the auditory P3 amplitude has been observed to be inversely correlated with illness duration<sup>10,14</sup> and, hence, may potentially track the operation of a putative progressive or neurodegenerative process across the illness course,<sup>40,41</sup> we recruited patients varying greatly in illness duration to attempt to replicate this observation in the present study.

## METHODS

### SUBJECTS

Participants consisted of 22 patients, with schizophrenia or schizoaffective disorder diagnosed according to *DSM-IV* criteria,<sup>42</sup> and 22 age-matched healthy control subjects (**Table 1**). All subjects provided written informed consent. Patients were recruited from psychiatric facilities affiliated with the University of North Carolina at Chapel Hill. Diagnoses were established by using the Structured Clinical Interview for *DSM-IV* administered by a psychiatrist or trained research assistant. Patients were functioning fairly well—most (82%) were outpatients—and they generally volunteered to participate in more than 1 study, including a functional magnetic resonance imaging study.<sup>43</sup> Clinical symptom ratings, assessed by using the Positive and Negative Syndrome Scale, indicated that the patients manifested relatively mild symptoms at the time of testing (Table 1); Positive and Negative Syndrome Scale data were missing for 3 patients.

Estimates of illness duration, defined as current age at testing minus estimated age at illness onset, indicated that the mean illness duration was relatively short (<6 years), but the variability within the group was large (Table 1). The group consisted of 7 individuals with first-episode schizophrenia, who had only recently experienced their first illness episode and had been ill for less than 1 year (mean ± SD, 0.4 ± 0.3 years), 7 individuals with an illness duration between 1 and 5 years (mean ± SD, 3.0 ± 1.9 years), and 6 individuals with chronic (>10 years) schizophrenia (mean ± SD, 15.7 ± 3.8 years); estimates of age at onset were not available for 2 patients.

At the time of testing, 18 patients were taking atypical antipsychotic medication, 2 patients were taking a combination with typical neuroleptic medications, 1 patient was prescribed medication but reported to be not compliant, and 1 patient was medication free. Most (59%) of the patients also had prescriptions for antidepressive, anticonvulsive, lithium carbonate, and/or antianxiety medications. Any patient with a history of neurological insult or illness, serious head injury, mental retardation, uncorrected vision or hearing problems, or current (<1 month before study participation) alcohol or drug dependence or abuse was excluded. Four patients had a history of alcohol and/or drug abuse.

Healthy control subjects were recruited by means of advertisements, and we used the same exclusion criteria, with the

**Table 2. Stimulus Events, Latency Intervals, and Scalp Locations Used for Quantification and Statistical Analysis of the ERP Component Amplitude Data\***

ERP Component	Stimulus Event	Latency Interval, ms	Scalp Locations†
Visual modality			
P1	Attended standard	90-140	O
N1	Attended standard	90-140	F, FC, C, CP, P
P2	Attended standard	190-240	F, FC, C, CP, P
N2	Attended novel	250-325	F, FC, C, CP
Target P3	Attended target	350-500	F, FC, C, CP, P
Novelty P3	Attended novel	350-500	F, FC, C, CP, P
Auditory modality			
N1	Unattended standard	75-125	F, FC, C, CP, P
P2	Unattended standard	150-200	F, FC, C, CP, P
MMN	Unattended deviant-minus-standard	100-250	F, FC, C, CP, P
N2	Attended target	200-275	F, FC, C
Target P3	Attended target	300-450	F, FC, C, CP, P

Abbreviations: C, central; CP, centroparietal; ERP, event-related potential; F, frontal; FC, frontocentral; MMN, mismatch negativity; O, occipital; P, parietal.

\*Amplitudes were quantified at each electrode as the mean voltage across the indicated poststimulus interval.

†F indicates electrode locations F7, F3, Fz, F4, and F8; FC indicates FT7, FC3, FCz, FC4, and FT8; C indicates T7, C3, Cz, C4, and T8; CP indicates TP7, CP3, CPz, CP4, and TP8; P indicates P7, P3, Pz, P4, and P8; and O indicates O1, Oz, and O2.<sup>44</sup>

addition of no personal and family history of major psychiatric disorder and no current or past alcohol or drug dependence or abuse. The 2 groups did not differ significantly in mean age ( $P > .98$ ), proportion of female subjects ( $P > .73$ ), and proportion of right-handed subjects ( $P > .17$ ), but years of education were significantly fewer in patients (Table 1). However, education was not significantly associated with the performance or ERP measures.

#### EXPERIMENTAL PROCEDURE

The ERPs were recorded by using a visual and auditory oddball paradigm. In the visual paradigm, subjects were instructed to attend to a series of visual stimuli, while ignoring a series of intermixed auditory stimuli. The visual stimuli ( $n = 1428$ ,  $25.4^\circ$  width,  $18.8^\circ$  height, 506-millisecond duration) consisted of standard stimuli (squares, 94.4% of all visual stimuli), target stimuli (circles, 2.9% of all visual stimuli), and novel stimuli (pictures of familiar objects, 2.7% of all visual stimuli) and were presented at a constant interstimulus interval of 1500 milliseconds. The auditory stimuli ( $n = 1428$ , 85 dB sound pressure level, 100-millisecond duration, 10-millisecond rise/fall) consisted of standard stimuli (1000-Hz tones, 97.1% of all auditory stimuli) and deviant stimuli (1064-Hz tones, 2.9% of all auditory stimuli) and were presented binaurally at a variable interstimulus interval of 1300 to 1700 milliseconds.

The subject's task was to attend to the visual stimuli, while ignoring the auditory stimuli, and to make a button-press response with the right index finger each time a visual target stimulus was presented. Subsequently, subjects performed an auditory oddball task in which they attended to auditory stimuli, while passively viewing visual stimuli. The auditory stimuli ( $n = 492$ ) were the same tones as those used in the prior blocks, consisting of standard (91.5% of all auditory stimuli) and deviant (8.5% of all auditory stimuli) target stimuli presented binaurally at a constant interstimulus interval of 1500 milliseconds. The visual stimuli (squares,  $n = 492$ , 100% of all visual stimuli) were presented at a variable interstimulus interval of 1300 to 1700 milliseconds. The subject's task was to attend to the auditory stimuli, while ignoring the visual stimuli, and to make a button-press response with the right index finger each time an auditory target stimulus was presented.

#### ELECTROPHYSIOLOGICAL RECORDING

Electroencephalograms (EEGs) were recorded from 30 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz, and O2.<sup>44</sup> The right mastoid served as the reference and AFz as the ground. Eye movements and blinks were measured with bipolar recordings of the vertical and horizontal electro-oculogram by using electrodes above and below the right eye and on the outer canthus of each eye, respectively. The EEG and electro-oculogram were amplified, bandpass filtered between 0.15 and 70 Hz (notch filter at 60 Hz), and digitized at 500 Hz.

#### DATA PROCESSING

Performance measures consisted of the proportion of correctly detected target stimuli (hit rate), the proportion of stimuli incorrectly responded to as target stimuli (false-alarm rate), and the time needed to respond to target stimuli (reaction time). The EEG recordings associated with incorrect behavioral responses or containing voltages in excess of  $\pm 100 \mu\text{V}$  were excluded. Ocular artifacts were controlled for by using regression analysis.<sup>45</sup> The ERPs were computed for each stimulus type at each scalp location; the averaging epoch included a 200-millisecond prestimulus baseline period and a 1000-millisecond poststimulus period. The ERPs were low-pass filtered at 15 Hz before quantification.

The ERP components were assessed only in those experimental conditions and only at those scalp locations where they were most clearly present (eg, being most likely uncontaminated by other overlapping potentials) and could be most reliably quantified (Table 2). Additional information on the ERP component amplitudes at other scalp locations can be found at [www.nirl.unc.edu](http://www.nirl.unc.edu). Amplitudes were quantified by computing the mean voltage across the latency range during which the component of interest was maximal. In addition to mean voltage measures, we obtained baseline-to-peak voltage measures for estimating the component amplitudes. Although mean amplitude measures were based on multiple data points, whereas peak measures were based on only a single data point, the mean and peak amplitude measures were strongly correlated and yielded essentially the same results. In this study, only the re-

sults based on mean voltage measures are presented. The ERP component peak latencies were quantified by detecting the most positive or negative peak within a specified time window at selected midline locations. For MMN, a statistical onset latency measure was also obtained by determining the time point at which the deviant-minus-standard difference wave started to deviate significantly from zero.<sup>46</sup>

### STATISTICAL ANALYSIS

Independent-sample *t* tests were used to assess between-group differences in the performance and ERP latency data. Two types of analyses were performed on the ERP amplitude data. The first was conventional analyses that involved (1) independent-sample *t* tests to assess between-group amplitude differences only at the midline location where the component of interest is typically largest and (2) 2-way (2 groups [between] × 3 anterior-to-posterior midline [Fz, Cz, Pz] electrode locations [within]) repeated-measures multivariate analyses of variance (MANOVAs) to assess group amplitude and topographic differences across the midline. The second was 3-way (2 groups [between] × 5 anterior-to-posterior midline electrode locations [within] × 5 lateral-to-medial coronal electrode locations [within]) repeated-measures MANOVAs to assess group amplitude and topographic differences in greater detail. In the 3-way MANOVAs, the electrode location factors were arranged such that the coronal electrode chains were nested under the anterior-to-posterior locations (F7-F3-Fz-F4-F8 vs FT7-FC3-FCz-FC4-FT8 vs T7-C3-Cz-C4-T8 vs TP7-CP3-CPz-CP4-TP8 vs P7-P3-Pz-P4-P8), which yielded 2 orthogonal electrode factors.

Follow-up tests included tests of simple main effects, simple interaction effects, and simple, simple main effects, and the Bonferroni approach was used to control for type I errors at the .05 level.<sup>47</sup> If a significant group-by-electrode location interaction emerged, the test was repeated on normalized data to determine whether the group-by-electrode interaction reflected real differences in topographic profile or simply differences in overall amplitude between groups.<sup>6,24,48</sup> Finally, topographic maps were constructed to provide a simple visual means of illustrating the various topographic patterns. Values in the text represent the mean ± SD. The effect size index,  $\eta^2$ , is also reported. Two-tailed statistics were used.

Within-group correlation and regression analysis was performed to assess the relationship between P3 and illness duration.<sup>10,14</sup> Also, we explored the relationships between sensory-evoked and cognitive-related ERP components and the relationships of P3 with symptom severity,<sup>25,13</sup> age,<sup>14</sup> and performance.<sup>46</sup> For all within-group analyses, significance levels were not corrected for multiple testing to maintain sufficient power to detect an individual, potentially relevant, true effect, if existing, in the data. Analyses were restricted to the midline electrode where the component of interest was maximal.

## RESULTS

### BEHAVIORAL DATA

In the visual task, patients showed a longer reaction time to target stimuli than did control subjects (573 ± 84 milliseconds vs 501 ± 87 milliseconds;  $t_{42} = 2.8$ ,  $P = .008$ ); no significant between-group differences were observed in the hit rate (91.2% ± 15.8% vs 95.5% ± 7.6%;  $P > .26$ ). In the auditory task, patients displayed a lower hit rate than did control subjects (86.2% ± 15.9% vs 96.8% ± 7.0%;  $t_{42} = 2.9$ ,  $P = .006$ ), with no group differences seen in re-

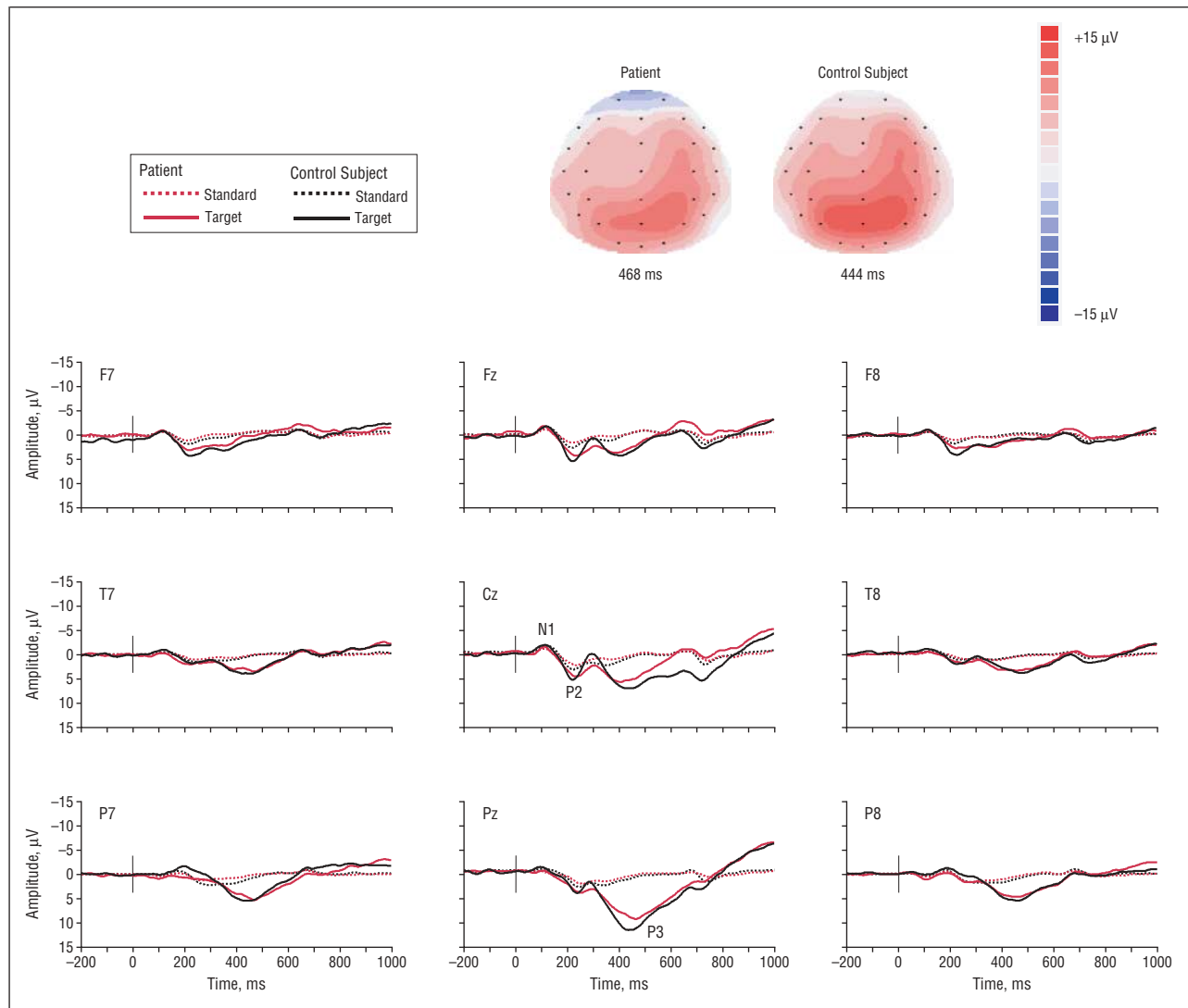
action time (498 ± 91 milliseconds vs 445 ± 110 milliseconds;  $P > .09$ ). In both tasks, false-alarm rates were low (<0.5%) and did not differ according to group.

### ELECTROPHYSIOLOGICAL DATA

**Figure 1** illustrates the visual-evoked N1 and P2 and the P3 elicited specifically by visual target stimuli. The N1 was accompanied by P1 localized over the occipital scalp (data not shown). **Table 3** presents for each group the quantified component latencies and amplitudes at a selected midline electrode and the results of the corresponding statistical analyses. No significant between-group differences were observed in the latencies, topographies, and amplitudes of P1, N1, and P2. In each group, P1 was maximal occipitally, whereas N1 and P2 were maximal at medial central and frontocentral locations. Additionally, P3 latency and amplitude at Pz did not differ significantly between groups (Table 3). Similarly, MANOVAs yielded no significant main effects of or interactions with group ( $P > .20$  for all), which indicates that no systematic group differences existed in P3 topography and amplitude. In each group, the visual target P3 was maximal at medial parietal locations and showed left-smaller-than-right asymmetries at medial frontocentral, central, and centroparietal sites.

**Figure 2** illustrates N2 and P3 elicited by visual novel stimuli. No significant group differences were observed in the N2 latency, topography, and amplitude. In each group, N2 exhibited a relatively symmetrical distribution, being maximal across medial frontal and central locations. For P3, no group differences were observed in peak latency, but patients manifested a significantly smaller amplitude at Pz than did control subjects (Table 3). The strength of the observed group-P3 relationship, as assessed by  $\eta^2$ , was moderate to strong, with the group factor accounting for 10% of the variance. Additionally, 3-way MANOVA yielded a significant group-by-coronal electrode interaction effect (Wilks  $\Lambda = .68$ ,  $F_{4,30} = 4.40$ ,  $P = .005$ ). This result reflected that group differences were largest at midline and left-medial locations, but results of follow-up tests did not exceed Bonferroni-adjusted significance levels. No other significant P3 amplitude or topographic differences were noted. In each group, the novelty P3 was bilaterally symmetrical and largest at medial parietal locations.

**Figure 3** presents N1 and P2 elicited by auditory standard and deviant stimuli recorded during visual attention. No significant group differences were observed in latencies, topographies, and amplitudes of N1 or P2 elicited by standard stimuli. In each group, N1 and P2 were maximal at medial frontocentral, central, and centroparietal locations. Additionally, the auditory deviant stimuli relative to the standard stimuli elicited in each group a prominent negativity, the MMN, which overlapped N1 and P2 and was most distinct between about 100 and 250 milliseconds after the stimulus onset (Figure 3 and **Figure 4**). An initial 2-way (2 groups × 2 stimulus types) analysis of variance on the unsubtracted data from Fz demonstrated that the effect of stimulus deviance, as reflected by MMN, was significant (stimulus type,  $F_{1,42} = 87.14$ ,  $P < .001$ ) and did not vary by group (group-



**Figure 1.** Event-related potentials to attended visual standard and target stimuli at frontal, central, and parietal scalp locations, superimposed for patients with schizophrenia ( $n=22$ ) and healthy control subjects ( $n=22$ ). Topographic maps of P3 to visual target stimuli are also illustrated. Electrode locations are indicated as black dots in the maps, and the numbers below each map indicate the time at which the maps were computed.

by-stimulus type,  $P > .60$ ), which provides statistical confirmation that the task-irrelevant auditory deviant stimuli elicited a significant MMN in both patients and control subjects. Analyses of the MMN time course and size at Fz revealed no significant group differences in peak latency or amplitude (Table 3), but the onset latency was longer in patients than in control subjects (110 vs 90 milliseconds). Similarly, MANOVAs produced no significant main effect of or interactions with group ( $P > .20$  for all), which suggests that no systematic group differences existed in MMN topography and amplitude. In each group, MMN exhibited a relatively symmetrical distribution, being maximal across medial frontal and central scalp.

**Figure 5** displays N2 and P3 elicited specifically by auditory target stimuli. No significant group differences were detected in N2 latency, topography, and amplitude. In each group, N2 was maximal across medial frontal and centroparietal scalp and exhibited a left predominance at medial central and centroparietal locations. Additionally, no group differences were estab-

lished in the auditory P3 latency, but patients exhibited a significantly smaller amplitude at Pz than did control subjects (Table 3). Also, 2-way MANOVA produced a significant group-by-midline electrode interaction effect (Wilks  $\Lambda = .82$ ,  $F_{2,42} = 4.60$ ,  $P = .016$ ), which signifies that group differences were larger at Pz and Cz than at Fz. Despite these amplitude differences, MANOVA performed on normalized data demonstrated that the P3 topographical profile across the midline did not differ according to group.

To assess topographic differences in greater detail, 3-way MANOVA was conducted and yielded a significant 3-way (group-by-coronal-electrode-by-midline-electrode, Wilks  $\Lambda = .41$ ,  $F_{16,27} = 2.39$ ,  $P = .022$ ) interaction effect. Simple interaction effects tests showed that the group-by-coronal electrode interaction effect was significant for the centroparietal (Wilks  $\Lambda = .64$ ,  $F_{4,39} = 5.60$ ,  $P = .001$ ) and parietal (Wilks  $\Lambda = .65$ ,  $F_{4,39} = 5.28$ ,  $P = .002$ ) data, while approaching Bonferroni-adjusted significance levels for the central data (Wilks  $\Lambda = .75$ ,  $F_{4,39} = 3.18$ ,  $P = .024$ ). These interactions reflected that P3 reduc-

**Table 3. Event-Related Potential Component Peak Latency and Amplitude Data at Selected Midline Electrode Locations as a Function of Group and Results of Statistical Analysis\***

Event-Related Potential Component (Electrode)	Patients (n = 22)		Control Subjects (n = 22)		Independent-Sample $t_{42}$ Test (2-tailed)					
	Latency, ms	Amplitude, $\mu\text{V}$	Latency, ms	Amplitude, $\mu\text{V}$	Latency			Amplitude		
					t Value	P Value	Effect Size, $\eta^2$ †	t Value	P Value	Effect Size, $\eta^2$ †
Visual modality										
P1 (Oz)	121 ± 24	1.3 ± 1.1	120 ± 27	0.7 ± 1.9	0.2	.822	0	1.3	.204	0.04
N1 (Cz)	124 ± 25	-1.1 ± 1.2	122 ± 17	-1.7 ± 1.0	0.3	.734	0	1.8	.074	0.07
P2 (Cz)	223 ± 25	1.8 ± 1.8	222 ± 20	2.7 ± 1.7	0.3	.802	0	1.7	.090	0.07
N2 (Fz)	301 ± 40	-0.6 ± 3.5	286 ± 35	-1.9 ± 2.8	1.3	.187	0.04	1.4	.185	0.04
Target P3										
(Pz)	476 ± 70	8.1 ± 4.2	444 ± 56	10.1 ± 6.5	1.7	.093	0.07	1.2	.224	0.04
(Fz)	454 ± 76	2.8 ± 3.7	427 ± 59	3.4 ± 5.4	1.3	.192	0.04	0.4	.664	0.01
Novelty P3										
(Pz)	478 ± 83	4.1 ± 3.7	466 ± 55	6.8 ± 4.4	0.6	.589	0.01	2.2	.034	0.10
(Fz)	490 ± 105	-0.4 ± 4.8	454 ± 65	1.1 ± 4.5	1.3	.186	0.04	1.0	.312	0.02
Auditory modality										
N1 (Cz)	100 ± 8	-2.4 ± 1.5	104 ± 11	-3.1 ± 1.4	1.2	.256	0.03	1.7	.103	0.06
P2 (Cz)	174 ± 23	1.2 ± 1.7	174 ± 17	0.6 ± 1.3	0	.988	0	1.3	.191	0.04
MMN (Fz)	190 ± 34	-2.4 ± 1.9	194 ± 35	-2.7 ± 1.7	0.4	.715	0	0.6	.565	0.01
N2 (Fz)	261 ± 30	-0.4 ± 3.1	244 ± 26	-1.9 ± 3.5	2.0	.057	0.08	1.5	.139	0.05
Target P3										
(Pz)	387 ± 62	6.7 ± 3.5	379 ± 46	10.8 ± 5.3	0.5	.618	0.01	3.0	.004	0.18
(Fz)	382 ± 59	1.2 ± 3.2	372 ± 44	4.2 ± 4.3	0.6	.554	0.01	2.6	.012	0.14

Abbreviation: MMN, mismatch negativity.

\*Data are given as mean ± SD.

†Traditionally,  $\eta^2$  values of 0.01, 0.06, and 0.14 represent small, medium, and large effects, respectively.

tions in patients were most pronounced at midline (Cz, CPz, Pz) and left-medial (C3, CP3, P3) locations ( $t_{42}=2.8-3.7$ ,  $P=.001-.008$ ,  $\eta^2=0.16-0.25$ ). Partial correlation coefficients for the Pz data demonstrated that the group-P3 relationship remained significant after group differences in auditory hit rate (partial correlation coefficient=0.32,  $P=.039$ ) or novelty P3 amplitude (partial correlation coefficient=0.31,  $P=.044$ ) had been statistically removed.

To determine whether the significant group-by-coronal electrode interactions reflected real differences in topographic profile or merely differences in overall amplitude between groups, similar MANOVAs were performed after the raw data had been normalized. These analyses demonstrated that the 2-way interaction remained significant for the central ( $P=.005$ ) and centroparietal ( $P<.001$ ) coronal electrodes. These results signified that patients displayed a left-smaller-than-right P3 asymmetry at the middle temporal (T7:  $2.4 \pm 2.3 \mu\text{V}$  vs T8:  $3.6 \pm 2.3 \mu\text{V}$ ,  $t_{21}=3.7$ ,  $P=.001$ ) and posterior temporal (TP7:  $3.1 \pm 2.3 \mu\text{V}$  vs TP8:  $4.2 \pm 2.2 \mu\text{V}$ ,  $t_{21}=4.1$ ,  $P=.001$ ) sites, whereas control subjects did not show such an asymmetry (T7:  $4.2 \pm 3.1 \mu\text{V}$  vs T8:  $4.3 \pm 2.6 \mu\text{V}$ ,  $P>.81$ ; TP7:  $4.6 \pm 3.0 \mu\text{V}$  vs TP8:  $4.8 \pm 2.6 \mu\text{V}$ ,  $P>.72$ ). No other significant amplitude or topographic differences were observed. In each group, the auditory P3 was maximal at medial parietal locations and showed left-smaller-than-right asymmetries at frontal and frontocentral sites, as well as at medial central and centroparietal locations.

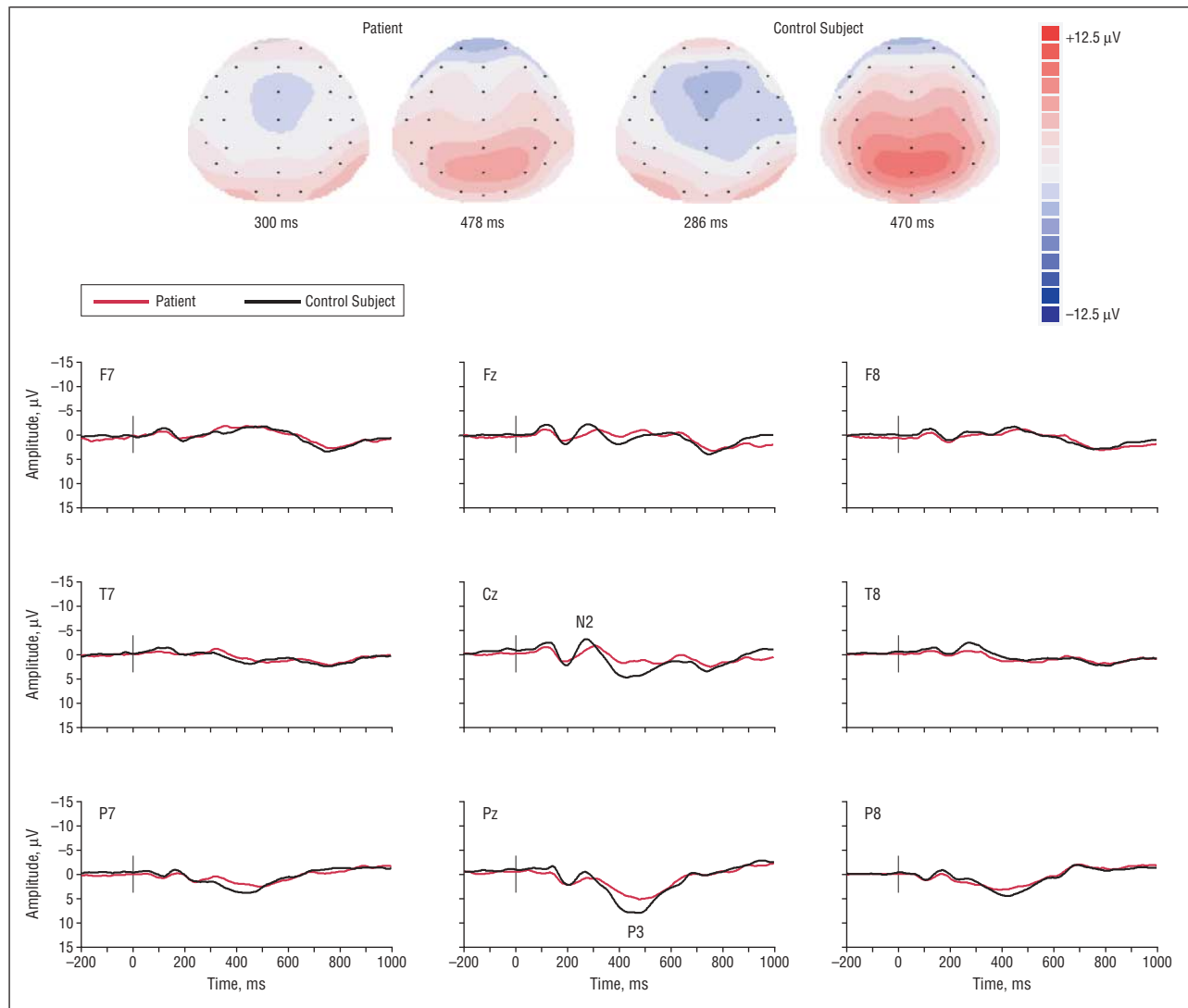
In patients, the auditory target P3 amplitude showed the anticipated correlation with illness duration (Figure 6). The visual target P3 amplitude also corre-

lated with illness duration ( $r=-0.49$ ,  $P=.030$ ). In contrast to the auditory P3 amplitude, the visual target P3 amplitude also correlated with age in patients ( $r=-0.54$ ,  $P=.009$ ,  $b=-0.24 \mu\text{V}/\text{y}$ ) and control subjects ( $r=-0.45$ ,  $P=.036$ ,  $b=-0.27 \mu\text{V}/\text{y}$ ). Given that age correlated strongly with illness duration ( $r=0.86$ ,  $P<.001$ ), these results indicated that the visual target P3 amplitude was associated more with normal aging than with illness duration.

In control subjects, P3 latency correlated with the reaction time and hit rate in both the visual and auditory modalities, whereas in patients these correlations were significant only in the visual modality (Figure 7). Furthermore, correlations between auditory sensory-evoked and cognitive-related ERP components were observed in control subjects but not in patients (Figure 7).

#### COMMENT

The strength of this study is that in it we assessed both sensory-evoked and cognitive-related ERP components and their relationships in both the visual and auditory modalities in patients with schizophrenia and healthy control subjects. The major finding is that patients showed smaller P3 amplitudes to visual novel stimuli and auditory target stimuli than did control subjects, whereas small or no significant between-group differences were observed in earlier-occurring ERP components. These data represent compelling evidence that high-level attention-dependent cognitive deficits central to schizophrenia do not originate from potential preceding deficits at lower levels of sensory, perceptual, or cognitive processing. The results support the view that schizophrenia is character-



**Figure 2.** Event-related potentials to attended visual novel stimuli at frontal, central, and parietal scalp locations, superimposed for patients with schizophrenia (n=22) and healthy control subjects (n=22). Topographic maps of N2 and P3 to visual novel stimuli are also illustrated. Electrode locations are indicated as black dots in the maps, and the numbers below each map indicate the time at which the maps were computed.

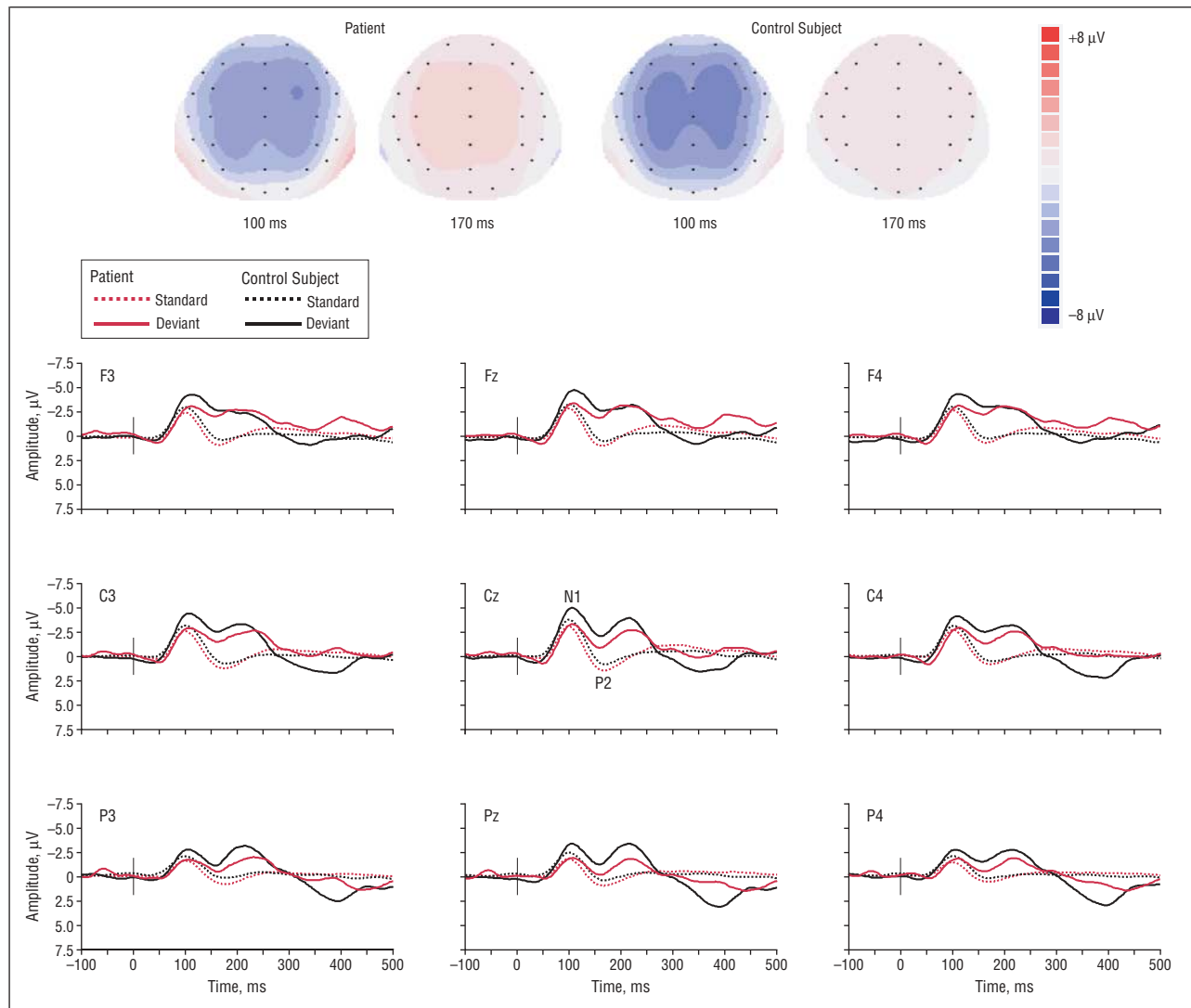
ized by fundamental deficits in integrative cortical functions that preferentially impair the ability to analyze, represent, and use stimulus context to guide behavior.<sup>22,23,49</sup>

The observation that the auditory P3 amplitude was associated with illness duration in patients replicates previous findings<sup>10,14</sup> and indicates that the auditory P3 reflects a basic pathophysiological process in schizophrenia that is present at illness onset and continues across the long-term course of the illness. These P3 data are in accord with the hypothesis that the pathophysiology of schizophrenia includes a progressive or neurodegenerative process that operates across the course of the illness in at least a subset of patients with schizophrenia.<sup>14,40,41</sup>

Another noteworthy finding is that in control subjects, P3 showed meaningful relationships to task performance in both the visual and auditory modalities, whereas in patients, significant P3-performance relationships were observed only in the visual modality. Similarly, significant correlations between auditory sensory-evoked and cognitive-related ERP components were

observed in control subjects but not in patients. These results suggest that, in the auditory modality, the functional links between perception, cognition, and action are uncoupled or weakened in schizophrenia. It has been hypothesized, indeed, that such functional disconnections between different levels of information processing in the brain underlie the auditory hallucinations and profound disintegration of thinking and action that characterize schizophrenia.<sup>50,51</sup> An important goal for future schizophrenia research, possibly with diffusion-tensor magnetic resonance imaging,<sup>52</sup> is to determine whether such functional disconnections are associated in vivo with structural disconnections of long intracortical white matter fiber tracts linking different brain regions, particularly those tracts connecting the temporal and frontal lobes.<sup>23,38,41,50-54</sup>

Patients exhibited a reduced auditory target P3, while manifesting a relatively normal visual target P3. Although a systematic comparison here between P3 to auditory and visual target stimuli is not possible because



**Figure 3.** Event-related potentials to auditory standard and deviant stimuli at frontal, central, and parietal scalp locations, recorded during visual attention, superimposed for patients with schizophrenia ( $n=22$ ) and healthy control subjects ( $n=22$ ). Topographic maps of N1 and P2 to auditory standard stimuli are also illustrated. Electrode locations are indicated as black dots in the maps, and the numbers below each map indicate the time at which the maps were computed.

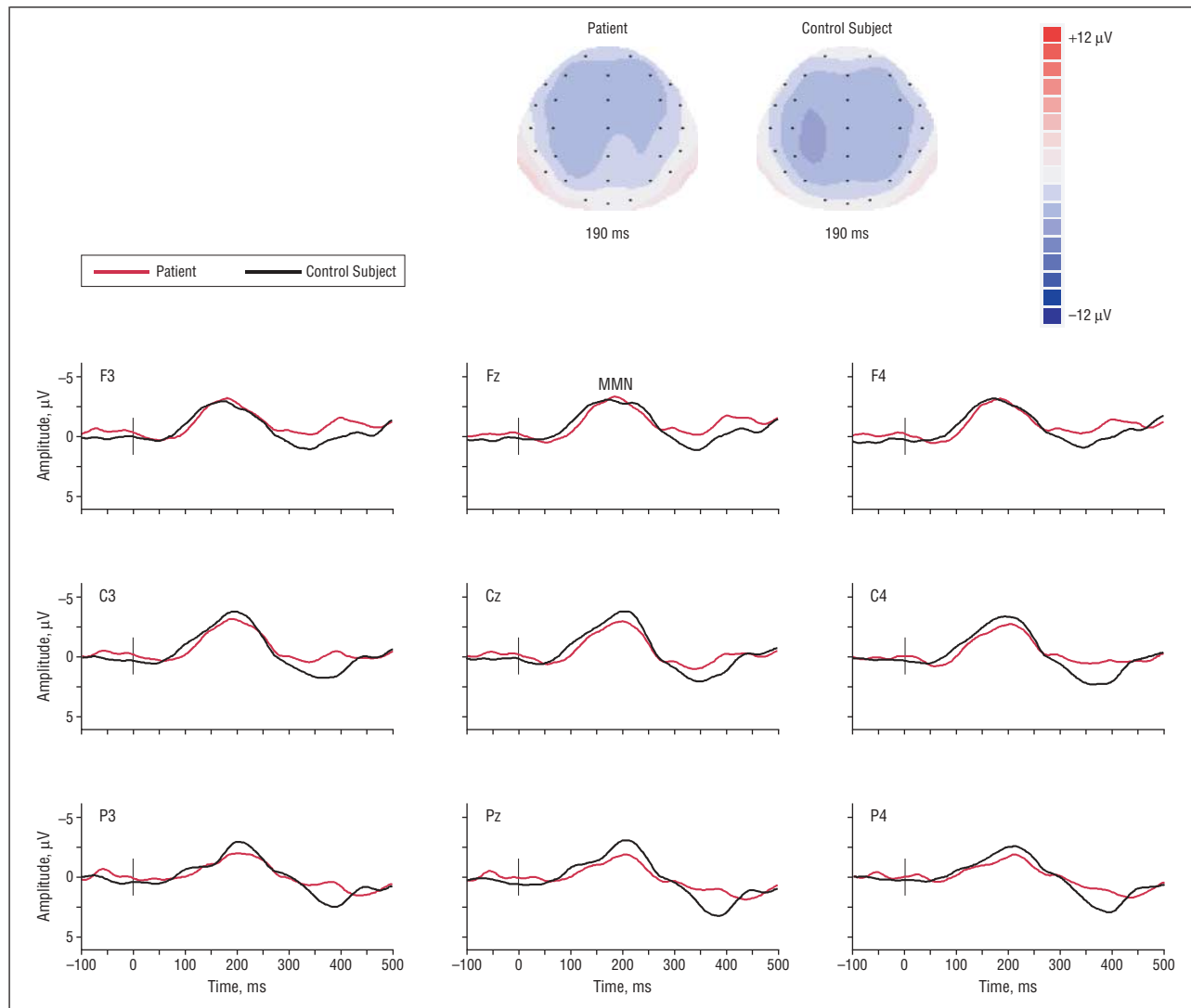
of marked differences in the eliciting experimental conditions, this finding adds to the evidence that the auditory target P3 is selectively or more severely impaired relative to the visual target P3 in schizophrenia.<sup>4,5,7,13</sup> This observation substantiates the notion that the auditory target P3 reflects a basic pathophysiological factor in schizophrenia, whereas the visual target P3 may index primarily the patient's current clinical state.<sup>4,7,13</sup>

The results that small or no between-group differences existed in ERP components preceding P3 are consistent with results of several studies<sup>15,31,55</sup> but are apparently not consistent with results of studies in which the authors report marked deficits in schizophrenia also in these earlier-occurring components, particularly the auditory P2<sup>5,25</sup> and MMN.<sup>31-36</sup> The apparent discrepancies among studies are probably related to differences in stimuli, task parameters, and patient samples. Specifically, the degree of stimulus deviance and the stimulus presentation rate are particularly important variables that determine whether patients with chronic schizophrenia show an impaired pitch-deviant MMN, with deficits more

readily demonstrated when the pitch difference between standard and deviant tones is large (eg,  $>10\%$ )<sup>34</sup> and/or when interstimulus intervals are short ( $<300$ - $400$  ms).<sup>35</sup> Although it is possible that different attentional strategies (ie, differential attention to the irrelevant auditory deviant stimuli) may confound MMN measurements in patients with schizophrenia and control subjects,<sup>31</sup> the effect of this variable, if any, seems minimal because the same between-group MMN results have generally been obtained regardless of whether a passive-ignore (eg, reading a book) or, as in the present study, an active-ignore (eg, performing a visual task) experimental procedure was used to direct subjects' attention away from the eliciting auditory stimuli.<sup>31-36</sup>

Another variable that does seem to be important is illness duration because pitch-deviant MMN reduction has been reported to be present in patients with chronic schizophrenia but to be absent in patients with first-episode schizophrenia.<sup>36</sup> Thus, our failure to detect MMN reduction in patients with schizophrenia is likely because we used a small pitch difference and a slow pre-





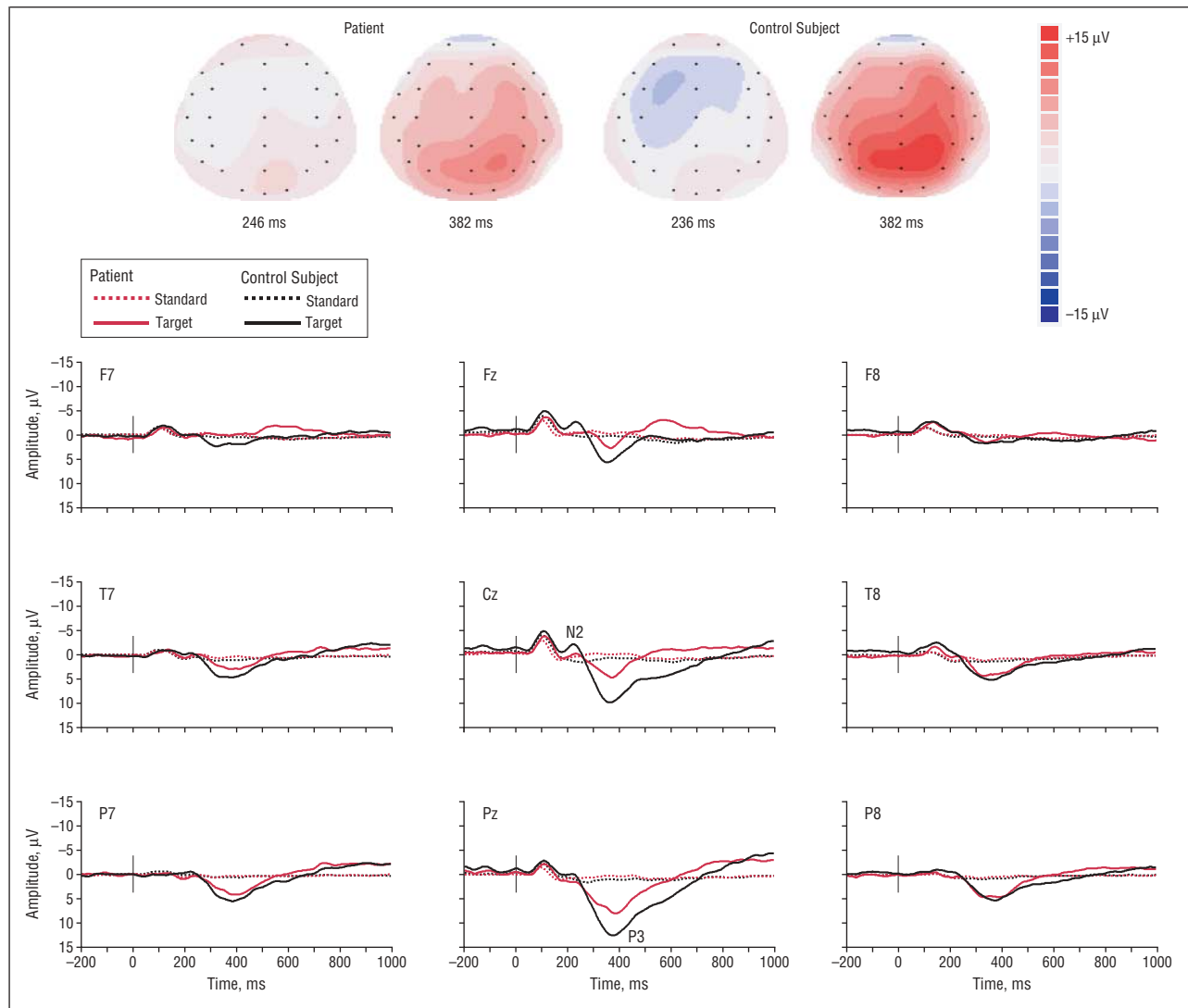
**Figure 4.** Auditory deviant-minus-standard event-related potential difference waves at frontal, central, and parietal scalp locations, recorded during visual attention, superimposed for patients with schizophrenia ( $n=22$ ) and healthy control subjects ( $n=22$ ). Topographic maps of mismatch negativity (MMN) are also illustrated. Electrode locations are indicated as black dots in the maps, and the numbers below each map indicate the time at which the maps were computed.

sensation rate to elicit MMN and because the average illness duration of the patient sample was relatively short. Indeed, the importance of the latter variable is underlined by the observation that, although we did not detect a significant overall correlation between MMN and illness duration ( $r=0.32$ ,  $P>.16$ ;  $n=20$ ), when we classified the patients into 2 distinct, though small, subgroups on the basis of having either first-episode, recent-onset ( $<1$  year;  $n=7$ ) or chronic ( $>10$  years;  $n=6$ ) schizophrenia, the MMN recorded in patients with chronic schizophrenia was 50% smaller than that observed in patients with first-episode schizophrenia (Fz:  $-1.4 \pm 2.3 \mu\text{V}$  vs  $-2.8 \pm 1.5 \mu\text{V}$ ,  $t_{11}=1.3$ ,  $P>.21$ ), who did not differ markedly from control subjects. The present data indicate that deficits in ERP components preceding P3 in patients with schizophrenia may not reflect primary pathophysiological features of the disease but may be related to illness chronicity or progression and/or consequential medication effects.

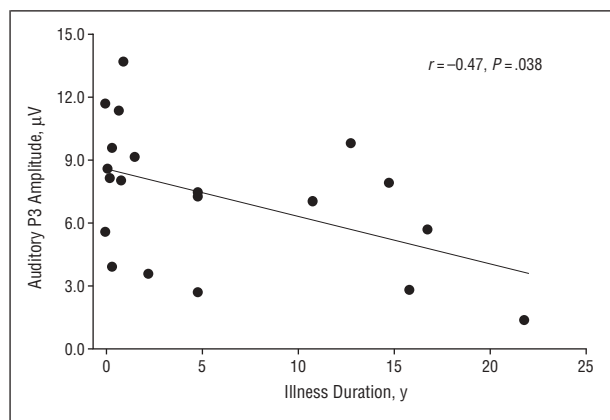
The observation that patients manifested a distinct left-smaller-than-right auditory P3 temporal scalp asym-

metry corroborates and extends results of previous studies<sup>6,15,24-28</sup> by indicating that this hemispheric asymmetry in schizophrenia is present only in the auditory, and not in the visual, modality. Because the left-lateralized auditory P3 deficit in schizophrenia has been linked to structural pathology of the left posterior superior temporal gyrus and the left planum temporale,<sup>6,27</sup> these findings support the concept that schizophrenia is characterized by abnormal lateralization of those cerebral functions and structures that mediate language and auditory processing.<sup>56</sup> The ERP data agree with evidence from neuroimaging and postmortem schizophrenia studies,<sup>23,37,38,41,43,49-54</sup> which implies that abnormalities in the function and structure of the temporal lobe and of its interaction with other, particularly prefrontal, regions represent a core element of the pathophysiology of schizophrenia.

It is important to acknowledge several limitations of the present study. Initially, the patient group was heterogeneous and group sizes were small, and the consequent loss of statistical power increases the probability

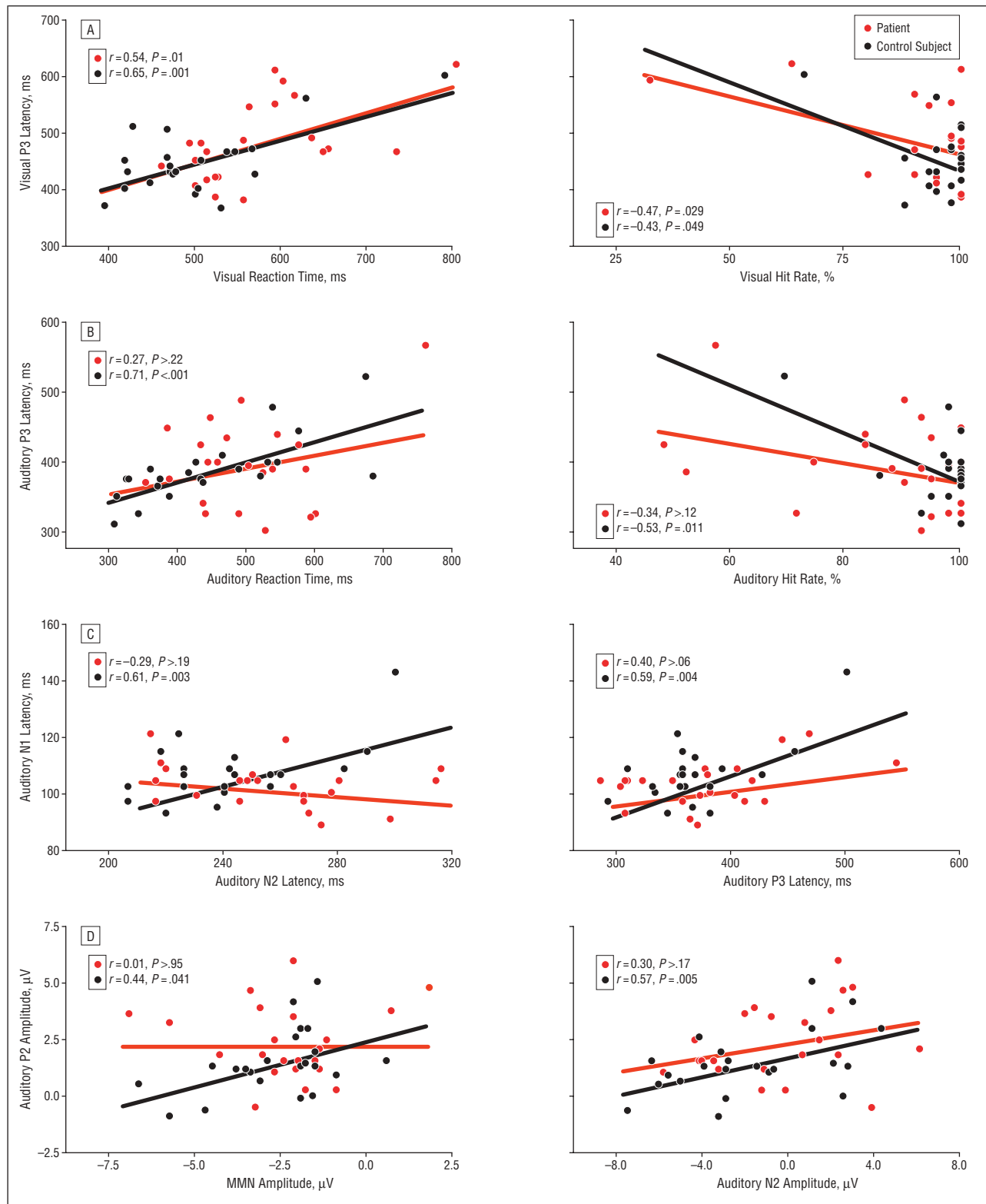


**Figure 5.** Event-related potentials to attended auditory standard and target stimuli at frontal, central, and parietal scalp locations, superimposed for patients with schizophrenia ( $n=22$ ) and healthy control subjects ( $n=22$ ). Topographic maps of N2 and P3 to auditory target stimuli are also illustrated. Electrode locations are indicated as black dots in the maps, and the numbers below each map indicate the time at which the maps were computed.



**Figure 6.** Scatterplot and least squares regression line illustrating the relationship between the auditory P3 amplitude and illness duration for patients with schizophrenia ( $n=20$ ). Illness duration data were missing for 2 of the 22 patients.

of type II errors, which yields an essential ambiguity concerning findings that were not significant. Similarly, the within-group analyses involved many tests while significance levels were not corrected for multiple testing, which increases the probability of type I errors. Accordingly, the results of particularly the exploratory correlational analyses should be considered in need of replication. Moreover, the patients originated predominantly from an outpatient setting and exhibited relatively mild symptoms at the time of testing, so they may not accurately represent individuals typically encountered in clinical practice or examined in previous schizophrenia studies, which may limit the generalizability and comparability of the present findings. Furthermore, almost all patients were taking psychotropic medications at the time of testing, so some of the findings obtained may reflect secondary effects of medication. Finally, the study was cross-sectional; therefore, the interpretation that the auditory



**Figure 7.** Scatterplots and least squares regression lines illustrating the relationships between P3 and behavioral performance (A and B) and between auditory sensory-evoked and cognitive-related event-related potential components (C and D) for patients with schizophrenia ( $n=22$ ) and healthy control subjects ( $n=22$ ).

P3 may index progressive brain changes in schizophrenia needs to be substantiated with longitudinal data.

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