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The Time Course of Visuospatial Processing Deficits in Schizophrenia: An Event-Related Brain Potential Study

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Event-related brain potentials (ERPs) were recorded during a dot enumeration task so as to investigate electrophysiologic correlates of early visuospatial processing in schizophrenia. Twenty-eight patients having a diagnosis of schizophrenia (n = 19) or schizoaffective disorder (n = 9) and 28 controls were tested. Patients showed poorer dot enumeration than did controls and also had markedly reduced early negative ERPs, which began about 150 ms after stimulus onset at the peak of the N1 potential and reached its maximum about 275 ms at the N2 peak. The N1 reduction in patients was greatest over left parietal sites for stimuli in the right visual field. The marked N1 and N2 reductions in patients are supportive of models postulating deficits in early visuospatial attention and allocation of conceptual resources in schizophrenia.

Abnormalities of visual information processing in schizophrenia have been found in a variety of cognitive tasks measuring visuospatial attention (Carter, Robertson, Chaderjian, Celaya, & Nordahl, 1992; Posner, Early, Reiman, Pardo, & Dhawan, 1988), backward masking (M. F. Green & Nuechterlein, 1994; Saccuzzo & Braff, 1981), perceptual organization (Place & Gilmore, 1980; Rabinowicz, Opler, Owen, & Knight, 1996), span of apprehension (Asarnow, Granholm, & Sherman, 1991; Nuechterlein, Edell, Norris, & Dawson, 1986), and perception of stimulus location and trajectory (O'Donnell et al., 1996). The aim of recent research in this area has been to elucidate the processes underlying these cognitive deficits in schizophrenia and to identify their neurophysiologic substrates. Identifying the earliest stage of visual information processing at which a deficit occurs is particularly important because all subsequent processing stages may be adversely affected. Specifically, do abnormalities of visual information processing stem from a deficiency in early sensory registration of stimuli, in attending to stimuli at different locations in the visual field, or in higher order cognitive processing of the visual input? Some studies have found evidence of abnormalities of visuospatial attention in schizophrenia, which appear to occur in the first 100 to 200 ms following onset of visual stimuli (Posner et al., 1988). Other behavioral studies suggest that abnormalities of visual information processing in schizophrenia stem not from deficits in early sensory or perceptual representations but rather from a deficiency in allocation of conceptual resources to process the visual input (Knight, 1984, 1992; Rabinowicz et al., 1996).

More direct measures of the time course of brain activation during visual information processing are needed to strengthen inferences about the critical role of early attentional and later cognitive deficits in schizophrenia. Event-related brain potentials (ERPs) are ideal for this purpose because they are time-locked to the onset of visual stimuli, and they provide a continuous record of brain activity with a resolution in the millisecond range. ERP components that occur at different times after stimulus onset (e.g., P1, N1, N2, or P3) are thought to reflect different aspects of information processing (Pfefferbaum, Roth, & Ford, 1995). P1, which peaks about 100 ms after stimulus onset, represents early activation of visual cortex (Schroeder et al., 1995). N1, between 100 to 200 ms after stimulus onset, is associated with sensory processing and with direction of attention to the stimulus (Clark & Hillyard, 1996; Mangun, 1995; Näätänen & Picton, 1987). N2, between 200 and 300 ms, reflects a subsequent stage of processing during which conceptual resources are allocated and stimulus classification occurs (Ritter, Simson, & Vaughan, 1988). P3, between 300 and 500 ms, reflects later cognitive processes, such as stimulus evaluation (Donchin & Coles, 1988).

Although studies using auditory tasks have found reductions in the amplitude of ERP components in schizophrenia (Ford et al., 1994; McCarley et al., 1993; O'Donnell et al., 1993; Roth, Duncan, Pfefferbaum, & Timsit-Berthier, 1986), studies that have measured ERPs of schizophrenic patients during simple visual discrimination tasks have yielded inconsistent findings (Brecher, Porjesz, & Begleiter, 1987; Egan et al., 1994; Ford et al., 1994; Matsuoka, Saito, Ueno, & Sato, 1996). Moreover, few

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studies have examined ERPs of schizophrenic patients during more cognitively demanding visual tasks. In one such study, Strandburg et al. (1994) recorded ERPs of schizophrenic patients during a complex visual discrimination task, the span of apprehension, which requires detection of briefly exposed target letters surrounded by distractor letters. Schizophrenic patients showed poorer performance than did controls and displayed markedly smaller amplitude of a negative ERP component that peaked 250 ms after stimulus onset. An unresolved question is whether this reduced ERP negativity reflects poorer task performance or rather a specific physiologic abnormality in schizophrenia.

The present study takes advantage of the temporal resolution of ERPs to investigate the time course of visuospatial processing during a cognitively demanding dot enumeration task. In this task, two to six dots were briefly exposed to a participant's left or right visual field, and the participant made a judgment as to whether the number of dots matched a simultaneously presented central digit (Bruder et al., 1992). A deficit in early visuospatial attention in schizophrenia (e.g., Posner et al., 1988), such as in directing attention to the dot stimuli, would be expected to result in a reduction in the amplitude of the N1 potential. If, instead, the early visual information-processing deficits in schizophrenia are related to a deficiency in allocation of conceptual resources (Giese-Davis et al., 1993; Knight, 1984, 1992), for instance, to estimate the number of dots and compare this number with the central digit, a reduction in the amplitude of the N2 component would be predicted. Finally, if the deficit is in later cognitive evaluation of the visual input, then a reduction in the P3 component should be found in schizophrenic patients.

Previous reports of inattention to the right hemispace in schizophrenia have been interpreted as evidence of left hemisphere dysfunction (Carter et al., 1992; Early, Haller, Posner, & Raichle, 1994; Posner et al., 1988; Tomer & Flor-Henry, 1989). The lateralized stimulus presentation used in the dot enumeration task also provides information about asymmetry of visuospatial processing. On the basis of the aforementioned findings, we predicted that behavioral and ERP abnormalities in schizophrenic patients would be greatest for dot stimuli in the right visual field.

Method

Participants

Twenty-eight patients from the Schizophrenia Research Unit of New York State Psychiatric Institute and 28 healthy controls were tested. The patients met criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV;* American Psychiatric Association, 1994) for schizophrenia (undifferentiated, $n = 12$; paranoid, $n = 4$; disorganized, $n = 3$), schizoaffective disorder, bipolar type ($n = 7$), or schizoaffective disorder, depressive type ($n = 2$).[1] The patient group included 18 men and 10 women, who ranged in age from 20 to 55 years ($M = 32.6$, $SD = 10.6$) and had a mean education level of 12.9 years ($SD = 3.4$). Research diagnoses were made on the basis of information provided from clinical interviews and from a semistructured interview by a trained and reliable rater using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). A consensus diagnosis was arrived at by the rater and a senior clinician (Xavier Amador). In addition, ratings of symptoms of patients were obtained using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and the Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Fishbein, 1992). At the time of testing, 25 of the patients were receiving antipsychotic medications: 9 patients were on haloperidol (mean dosage = 11 mg/day; range = 1–20); 8 patients were on risperidone (mean dosage = 5.8 mg/day; range = 3–9); 3 patients were on clozapine (mean dosage = 442 mg/day; range = 300–575), 3 patients were on prolixin (mean dosage = 23 mg/day; range = 20–30), 1 patient was on stelazine (40 mg/day), and 1 patient was on loxapine (40 mg/day). The remaining 3 patients (two schizophrenic and one schizoaffective, depressive type) did not receive antipsychotic medications for at least 14 to 24 days before testing.

The control participants were screened using a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Spitzer & Endicott, 1975) to exclude those with current or past psychopathology. This group consisted of 14 men and 14 women who ranged in age from 20 to 60 years ($M = 36.1$, $SD = 12.1$) and had a mean education level of 15.7 years ($SD = 1.8$). There was no significant difference in mean age between the patient and control groups, $F(1, 48) = 0.88$, $p = .35$, but the patient group had significantly less education than the controls, $F(1, 48) = 12.59$, $p = .001$. As indicated in the results, however, education was not significantly associated with either performance in the dot enumeration task or with ERP measures in this study.

All patients and controls were right-handed, as indicated by their laterality scores on the Edinburgh Inventory (Oldfield, 1971). They were screened to exclude those who had a history of neurological insult or illness, current substance abuse, or a history of substance abuse that obscured diagnosis.[2]

Dot Enumeration Task

ERPs were recorded during a modified version of the visual half-field dot enumeration task used in prior studies (Bruder et al., 1992; McClone & Davidson, 1973). At the beginning of each trial, participants viewed a moderately dense visual mask (random line pattern) with a central cross for 1 s. They were instructed to fixate on the central cross and not to move their eyes. The mask and fixation cross were replaced by a digit at central fixation and by two–six dots in either the right or left visual field. The exposure duration of the central digit and lateral dots was 180 ms. The mask and central cross then returned to the screen and remained on for 2.3 s. At the end of this period, the screen went blank, and the participant was required to press a response button if the number of dots matched the fixation digit. The length of the response period was 2.5 s. The delayed response was intended to reduce the influence of response-related motor potentials on the ERP measures.

[1] Preliminary analyses, using the same repeated measures ANOVA used to compare ERPs of the patient and control groups (see *Statistical Analyses of ERP Data* in Method), were performed to determine whether there were differences in ERPs between patients meeting criteria for schizophrenia ($n = 19$) or schizoaffective disorder ($n = 9$). There was no significant difference between the schizophrenia and schizoaffective groups in the amplitude of P1, N1, N2, P3, or slow wave—all $Fs(1, 26) < 1.77$, $p > .20$. The data of schizophrenic and schizoaffective patients were therefore pooled for the analyses reported in this article.

[2] An analysis was performed to evaluate whether ERPs of patients with a history of alcohol abuse ($n = 8$) differed from those of patients without a history of alcohol abuse ($n = 20$). Using the same repeated measures ANOVA used to compare patient and control groups, we found no significant difference between patients with and patients without a history of alcohol abuse in amplitude of P1, N1, N2, P3, or slow wave, all $Fs(1, 26) < 1.0$, $p > .45$. Moreover, all group differences reported for the full samples were confirmed when only patients without a history of alcohol abuse were included in the analyses.

Response hand was also counterbalanced across participants. On half of the trials, the number of dots was the same as the fixation digit, and on the other half of trials, the number of dots was one more or one less than the fixation digit. Each participant was tested in four blocks of 40 trials, in which dots were presented in the right visual field on half of the trials or the left visual field on the other trials. Visual field and condition (match, nonmatch) were pseudorandomized within each block, with no more than three consecutive repetitions of the same visual field.

The stimuli (mask, fixation cross, digit, and dots) were black on a light gray background. They were presented on a 15-in. (38.1-cm) monitor to a participant seated in a sound-attenuated booth (Industrial Acoustics Company, Bronx, NY). A chin rest was used to minimize head movements and to align the participant's eyes with the central fixation cross on the monitor screen, located 56 cm from the participant. The stimuli were generated using NeuroScan STIM software (NeuroScan, 1994). The position of the dots in the left or right field was determined by randomly assigning dots to squares in a grid, with the constraint that no two dots appeared in adjacent squares. Eight different grid sets were produced for each of the five possible numbers of dots (two to six). These sets and their mirror-reversals were used to yield 40 left and 40 right field stimuli. Visual field and dot number were equally represented within each block of 40 trials. The distance from the fixation digit to the near edge of the lateral field within which dots could appear subtended an angle of 3°8′. The distance from the digit to the far edge subtended an angle of 6°2′. The height of the field within which dots could appear subtended an angle of 7°5′.

Electrophysiological Recording and ERP Analyses

The scalp electroencephalogram (EEG) was recorded from 13 lateral pairs of electrodes (FP1,2; F3,4; F7,8; FC5,6; FT9,10; C3,4; T7,8; CP5,6; TP9,10; P3,4; P7,8; P9,10; O1,2) and from 4 midline electrodes (Fz; Cz; Pz; Oz) using an electrode cap (Electro Cap International, Inc., Eaton, OH) with a nose reference and an Fpz ground. Standard Beckman Ag/AgCl electrodes at supra- and infraorbital sites surrounding the right eye were used to monitor eyeblinks and vertical eye movements (bipolar), and electrodes at right and left outer canthi monitored horizontal eye movements (bipolar). All electrode impedances were below 5 kΩ. EEG was recorded through a Grass Neurodata acquisition system at a gain of 10 k (5 k for eye channels), with a 0.01–30 Hz band pass (−6 dB/octave). A NeuroScan EEG acquisition system acquired and digitized the data at 100 samples per second (NeuroScan, 1993). Data were sampled for 1,280 ms (200 ms prestimulus) and low pass filtered offline at 12.5 Hz (−24 dB/octave frequency domain filter) after electrooculogram (EOG) artifact removal.

EEG data were corrected for blinks on a trial-by-trial basis using a linear regression algorithm (Semlitsch, Anderer, Schuster, & Presslich, 1986). Epochs contaminated by eye movements or other movement-related artifacts were excluded from analyses offline using a rejection criterion of ±100 μV on any channel. Average ERP waveforms were computed for trials on which participants responded correctly to a match or nonmatch between the number of dots and the fixation digit for each visual field at each electrode for each participant, as well as across participants within each group. The average number of trials remaining after artifact removal for each condition was 21 (range = 8–34) for patients and 25 (range = 8–38) for controls. The effective number of trials entering into ERPs measures, after averaging over condition (match, nonmatch), was twice the aforementioned values.

After EOG artifact removal, small residual horizontal eye movements (HEOG) toward the stimulated visual field were present in most participants beginning around stimulus offset at about 180 ms, which approximates the average latency for saccadic eye movements (McKeever, 1986). Mean HEOG amplitudes were approximately −15 μV and +15 μV for stimulus presentations to the left and right visual field, respectively, and were equally present for controls and patients (see HEOG plots in Figures 1 and 2).[3] These horizontal eye movements primarily affected lateral frontal recording sites, gradually decreasing to zero from anterior to posterior sites. Because the size of the residual HEOG was small, they were best measured in averaged ERP waveforms rather than in single trial data. These small HEOG contributions to the EEG were corrected using standard linear regression methods (e.g., Verleger, Gasser, & Möcks, 1982). Transfer coefficients were computed during a separate calibration period from a few participants who were asked to fixate known locations in each visual field. The coefficients were optimized across the calibration participants and were trimmed so as to be equal in size but opposite in sign between hemispheres (i.e., the coefficients for left hemisphere sites were FP1 = .057, F7 = .167, F3 = .049, FT9 = .139, FC5 = .077, T7 = .072, C3 = .015, TP9 = .045, CP5 = .037, P9 = .034, P7 = .029, P3 = .017, O1 = .007; inverse coefficients were used for corresponding right hemisphere sites and zero coefficients for midline sites). These coefficients were found to be satisfactory in all cases; that is, residual HEOG artifacts were effectively reduced in the average ERP waveforms of each group.

The averaged ERP waveforms were submitted to a principal-components analysis (PCA) derived from the covariance matrix, followed by a varimax rotation, to determine the sources of variance in the ERP waveforms (Chapman & McCrary, 1995; Donchin, Kutas, & McCarthy, 1977; Kayser et al., 1997; Kayser, Tenke, & Bruder, in press). The factor analysis was computed using BMDP statistical software (BMDP4M; Dixon, 1992). Columns of the data matrix represented time (110 sample points from −100 ms to 1,000 ms), and rows consisted of participants (56), visual fields (2), conditions (2), and electrode sites (30). The number of orthogonal factors extracted by the PCA was limited by a criterion of eigenvalues greater than 1.0. Peak latencies of factor loadings and topographies of factor scores were used to identify five principal components extracted by the PCA, which together accounted for 86.1% of the ERP variance and corresponded to the following ERP components: P1 (peak latency 100 ms, occipital maximum, 1.9% explained variance), N1 (160 ms, lateral parietal maximum, 4.5%), N2 (260 ms, posterior midline maximum, 5.5%), P3 (420 ms, broad parietal maximum, 36.0%), and slow wave (860 ms, broad central maximum, 35.2%). Given the time course of these factor loadings, conventional ERP amplitudes with reference to a 100-ms prestimulus baseline were measured as average values within the following latency windows poststimulus: (a) P1, between 70 and 130 ms; (b) N1, between 140 and 220 ms; (c) N2, between 230 and 330 ms; (d) P3, between 340 and 550 ms; (e) slow wave, between 560 and 1,000 ms.

Analyses of Behavioral Data

The percentage of correct responses (i.e., when the participant responded to a match between the number of dots in the lateral field and the central digit) and the percentage of false alarms (i.e., when the participant responded but the number of dots in the lateral field was different from the central digit) were used to compute a signal detection accuracy measure d' (D. M. Green & Swets, 1966) for each visual field. An analysis of variance (ANOVA) of d' scores and percentage of correct responses evaluated group differences in accuracy for stimuli in the right and left visual fields.

[3] An ANOVA of the average HEOG amplitude in the time windows used to compute P1, N1, N2, P3, and slow wave amplitudes, with the factors Group, Visual Field, and Condition, did not reveal any significant difference in HEOG amplitudes between groups, all Fs(1, 54) < 1.72, $p > .20$; nor were there significant Group × Visual Field interactions, all Fs(1, 54) < 1.03, $p > .30$.

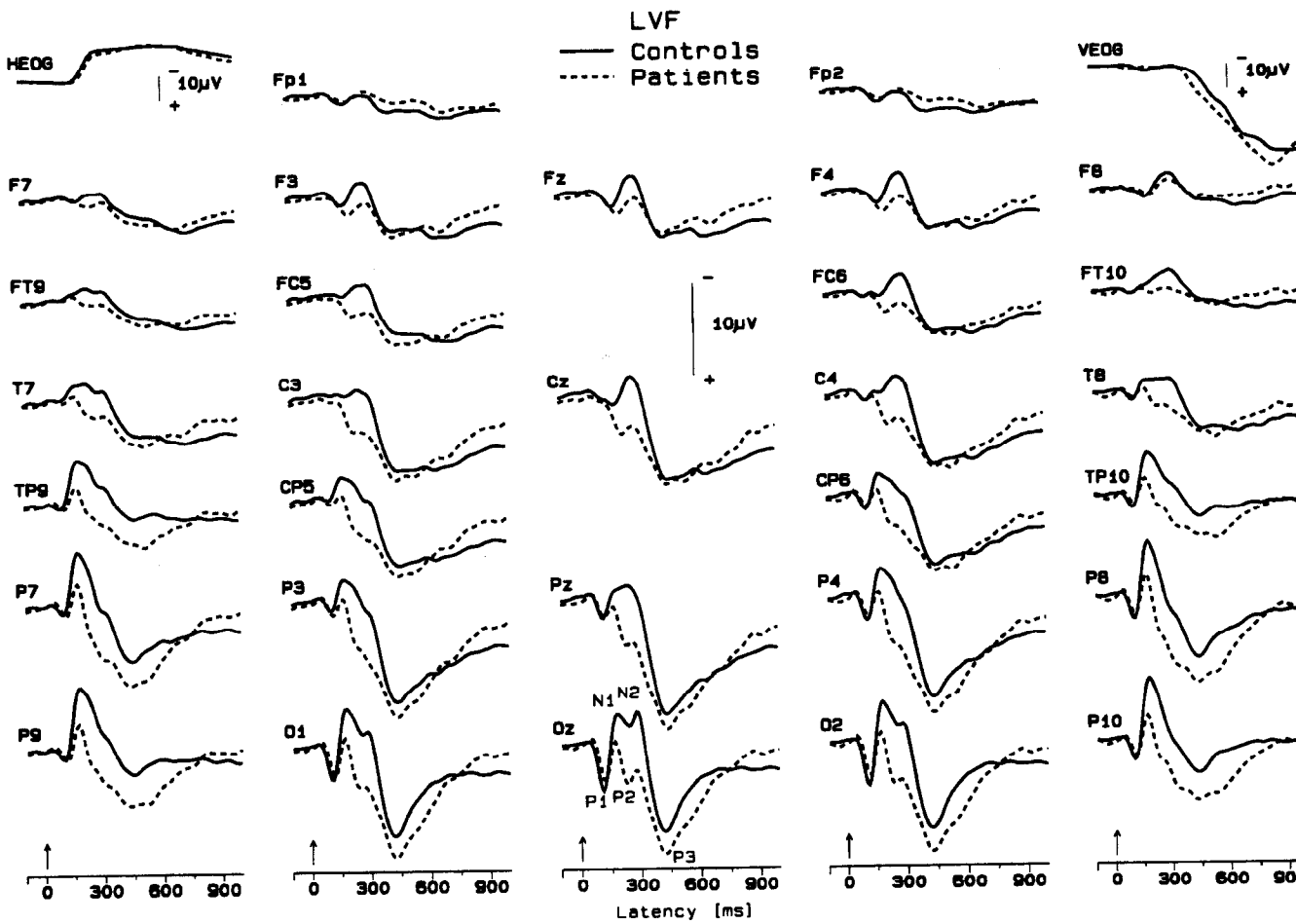

Figure 1. Grand average event-related brain potential waveforms of patients and controls to stimuli presented in the left visual field (LVF) for 30 scalp electrode sites (averaged across condition). Note the different scaling (in microvolts [μV]) of waveforms for horizontal eye movement (HEOG) and vertical eye movement (VEOG) channels showing data before artifact removal.

Statistical Analyses of ERP Data

Average amplitudes within the P1, N1, N2, P3, and slow wave latency windows and the corresponding PCA factor scores were subjected to repeated-measures ANOVA. Analyses of the average amplitudes for these components and the PCA factor scores generally yielded the same results. Only analyses of average amplitudes of P1, N1, N2, P3, and slow wave are therefore reported below, except where the ANOVA for PCA factor scores failed to confirm the results for these averages. Initial analyses evaluated group differences in amplitude at midline sites (Fz, Cz, Pz, and Oz). To reduce the amount of data in ANOVA of ERPs at sites over the two hemispheres and allow orthogonal groupings of electrodes spanning regions of interest, electrode sites were selected for comparing frontal (F3,4; F7,8), central (C3,4; T7,8), and parietal (P3,4; P7,8) sites at medial and lateral locations over the right and left hemispheres. These regional differences were represented in the ANOVA by variables for frontal-parietal (F, C, P), medial-lateral, and hemisphere. Visual field (left, right) and stimulus condition (match, nonmatch) were also included as additional repeated measures variables, although no effects related to stimulus condition are reported. Group (patient, control) was a between-subjects variable. F ratios were evaluated using degrees of freedom after Geisser–Greenhouse epsilon correction (Jennings & Wood, 1976) where appropriate to counteract heterogeneity of variance–covariance matrices associated with repeated measures. Significant interactions were examined through simple effects to locate the source of interaction. Only findings that reached a .05 significance level are considered in this report. Significant interactions involving frontal-parietal, medial-lateral or hemisphere were also confirmed after scaling the amplitudes across electrode sites (McCarthy & Wood, 1985).

Product–moment correlations were computed to examine the strength of the relationship between ERP measures, behavioral accuracy (d' scores averaged over visual field), and symptom scores on the PANSS and BPRS. Only ERPs at the midline parietal (Pz) site (averaged over match–nonmatch and visual field) were used to reduce the number of correlations. Correlations were also computed to examine the relation of accuracy and ERP measures to age and education. Significant correlations were validated using nonparametric Spearman rank-order correlations.

Results

Behavioral Performance

Differences in accuracy between group and visual field were evaluated using a 2 × 2 ANOVA of d' scores. Accuracy of dot

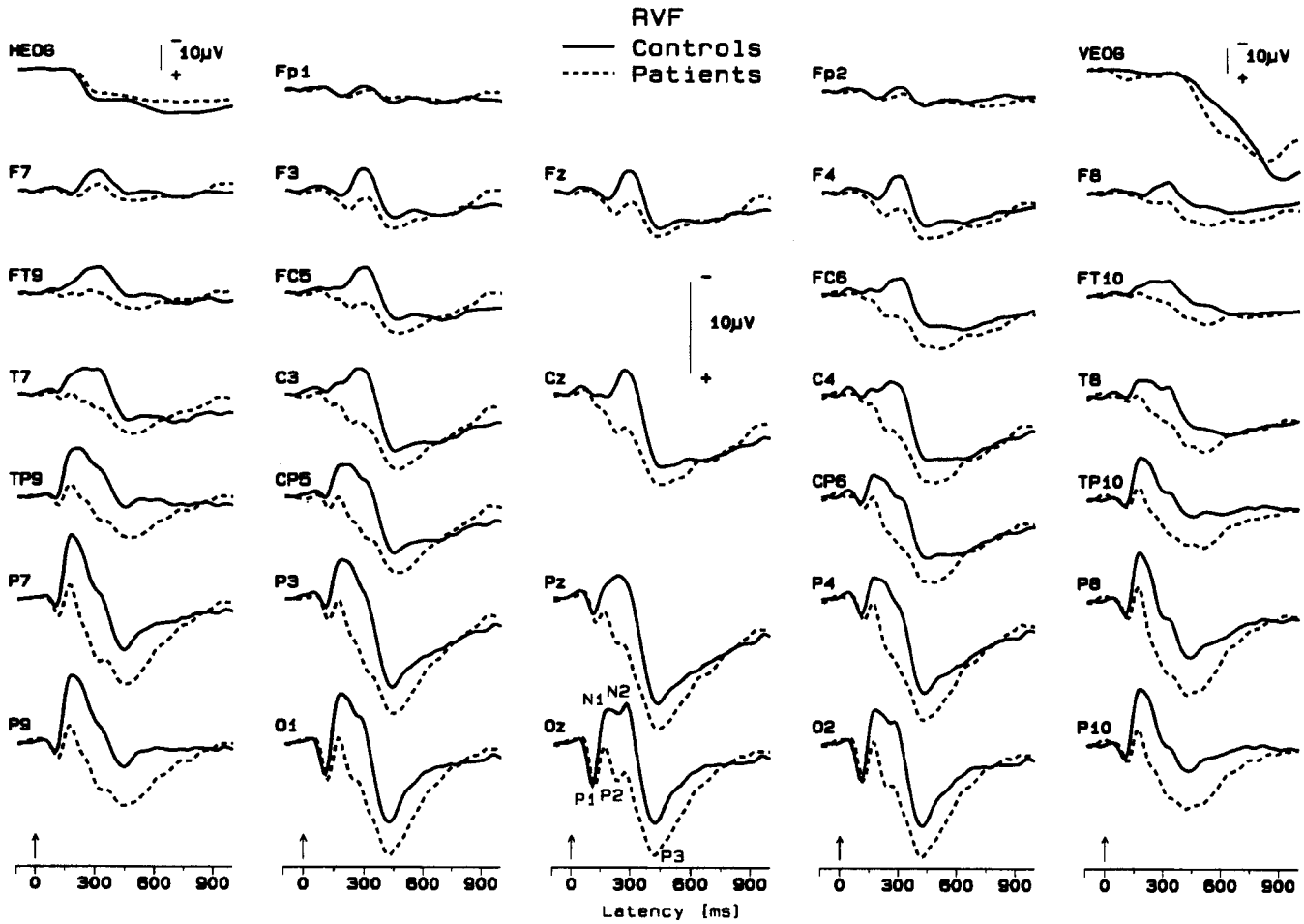

Figure 2. Grand average event-related brain potential waveforms of patients and controls to stimuli presented in the right visual field (RVF) for 30 scalp sites (averaged across condition). Note the different scaling (in microvolts [μV]) of waveforms for horizontal eye movement (HEOG) and vertical eye movement (VEOG) channels showing data before artifact removal.

enumeration was poorer in schizophrenic patients ($d' = 1.0$) than in controls ($d' = 1.4$), $F(1, 54) = 6.51, p = .01$. Likewise, the percentage of correct "match" responses was smaller in schizophrenic patients (66.6%) than in controls (73.5%), $F(1, 54) = 6.57, p = .01$. There was also a significant visual field effect, with accuracy being greater for dots in the left ($d' = 1.3$) than in the right ($d' = 1.1$) visual field, $F(1, 54) = 9.60$, $p < .01$, but there was no significant Group × Visual Field interaction.

ERP Data for Midline Sites

The middle column in Figure 1 and 2 shows the average ERP waveforms for schizophrenic patients and controls at the midline sites (Fz, Cz, Pz, Oz) for dot stimuli in the left or right visual field. The waveforms at the occipital site (Oz) illustrate the ERP components evident for each group—P1, N1, P2, N2, P3, and a late positive slow wave. The amplitude of P1 did not significantly differ between groups. The earliest group difference in the ERP waveforms began about 150 ms after stimulus onset, with patients having considerably less N1 amplitude than controls, $F(1, 54) = 16.03$, $p < .001$. The smaller negativity in patients was even more marked at N2, $F(1, 54) = 35.70$, $p < .0001$), which peaked at about 275 ms after stimulus onset. As can be seen in Figures 1 and 2, the group difference in N1 and N2 amplitude was present for dot stimuli in each visual field and was greatest at the posterior midline sites (Pz and Oz) where these potentials are prominent (Group × Frontal-Occipital interaction for N1, $F(3, 162) = 8.22$, $p < .01$, $\epsilon = .46$; and for N2, $F(3, 162) = 5.12$, $p = .01$, $\epsilon = .54$). There was no significant difference between groups in P3 or slow wave amplitude at the midline sites.

ERP Data for Left and Right Hemisphere Sites

ERP waveforms. Figures 1 and 2 also show the average ERP waveforms for medial and lateral sites over each hemisphere. P1 amplitude was largest at the medial-occipital sites (O1 and O2),

with both groups showing greater P1 amplitude over right than left hemisphere. As found for the midline sites, there was no difference between groups in P1 amplitude for the medial or lateral sites. N1 amplitude was largest at lateral-parietal sites, with patients showing considerably smaller N1 amplitude than controls. N2 was largest medially over central through occipital sites in controls, but patients showed little negativity in the N2 range. P3 amplitude was largest at medial-parietal sites, and patients appear to show greater positivity than controls in the P3 window, particularly at the lateral-parietal sites (e.g., at P7 and P8).

P1 amplitude. Figure 3 shows the mean P1 amplitude for each group at frontal, central, and parietal regions over each hemisphere. An ANOVA did not reveal a significant group main effect for P1 amplitude, $F(1, 54) = 0.18$, $p = .67$. There was a significant hemispheric asymmetry, with greater P1 amplitude over right than left hemisphere sites, $F(1, 54) = 31.79$, $p < .0001$. This P1 asymmetry was present in both controls, $F(1, 54) = 29.49$, $p < .0001$, and patients, $F(1, 54) = 6.47$, $p = .01$ (simple main effects of hemisphere at each group) but was larger in controls, Group × Hemisphere interaction, $F(1, 54) = 4.16$, $p < .05$. There was also a Group × Hemisphere × Frontal-Parietal interaction, $F(2, 108) = 6.06$, $p < .01$, $\epsilon = .75$. As can be seen in Figure 3, the P1 asymmetry in controls was greater over parietal than frontal regions, Hemisphere × Frontal-Parietal interaction, $F(2, 108) = 17.59$, $p < .0001$, $\epsilon = .75$, but the P1 asymmetry in patients did not differ across the three regions, $F(2, 108) = 0.51$, $p = .55$. Because P1 amplitude was largest at the medial-occipital sites (see O1 and O2 in Figures 1 and 2), an ANOVA was also performed using the P1 values at these two sites. This analysis confirmed the P1 asymmetry, $F(1, 54) = 12.58$, $p < .001$, and also the larger P1 asymmetry for controls than patients, Group × Hemisphere interaction, $F(1, 54) = 5.09$, $p < .05$.

N1 amplitude. There was a significant overall group difference in N1 amplitude, $F(1, 54) = 21.48$, $p < .0001$. The smaller N1 amplitude for patients than for controls was most evident over lateral-parietal sites where N1 was largest (see Figures 1 and 2), which is supported by a Group × Frontal-Parietal × Medial-Lateral interaction, $F(2, 108) = 14.61$, $p < .001$, $\epsilon = .70$. A Group × Hemisphere × Visual Field × Frontal-Parietal interaction was also found, $F(2, 108) = 10.90$, $p < .001$, $\epsilon = .76$, and this is illustrated in Figure 4. The four-way interaction stemmed from the presence of a significant Group × Hemisphere × Frontal-Parietal interaction for stimuli in the right visual field, $F(2, 108) = 7.59$, $p < .01$, $\epsilon = .70$, but not in the left visual field, $F(2, 108) = 0.72$, $p = .48$, $\epsilon = .94$. When stimuli were in the right visual field (right portion of Figure 4), controls showed a greater hemispheric asymmetry of N1 at parietal sites than at frontal sites (Hemisphere × Frontal-Parietal interaction), $F(2, 108) = 22.40$, $p < .0001$, $\epsilon = .70$, but patients did not (Hemisphere × Frontal-Parietal interaction), $F(2, 108) = 0.71$, $p = .45$. As can also be seen in Figure 4, controls showed greater N1 amplitude over the left than right parietal

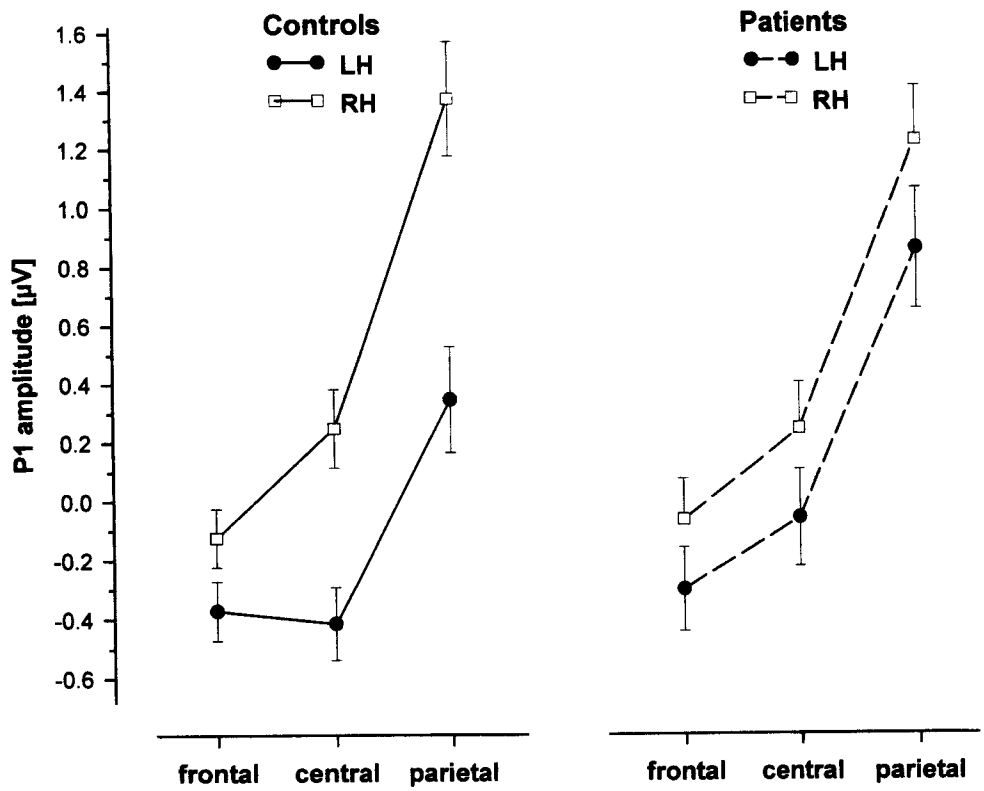

Figure 3. Means and standard errors of P1 amplitude (in microvolts [μV]) for patients and controls at frontal, central, and parietal sites over the left hemisphere (LH) and right hemisphere (RH).

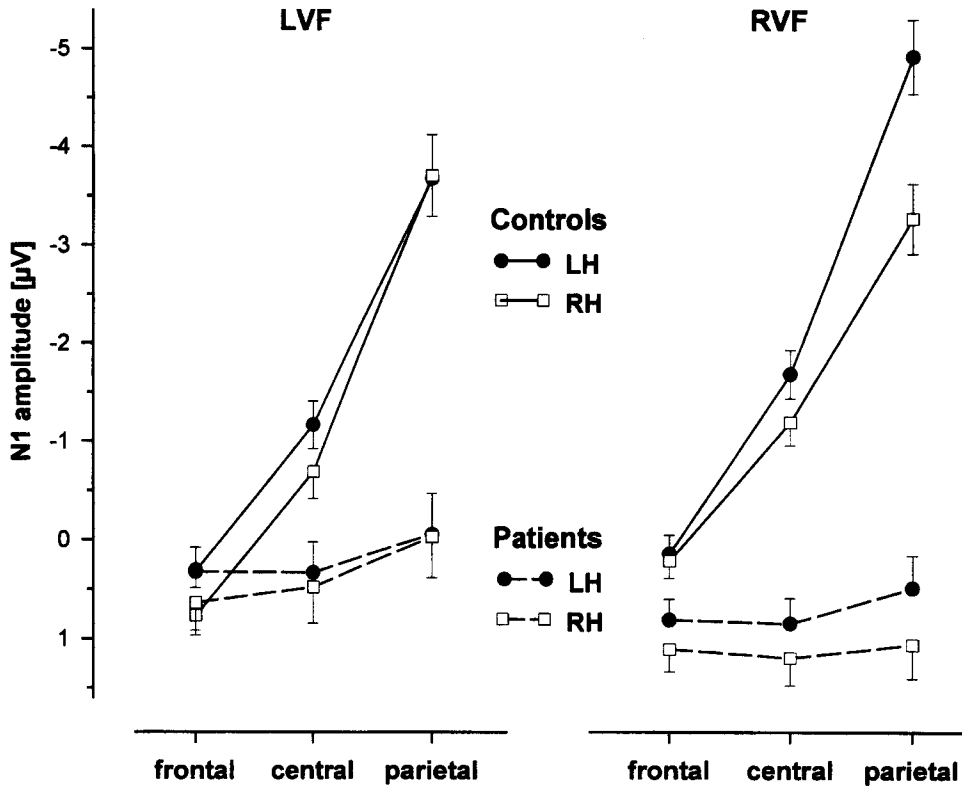

Figure 4. Means and standard errors of N1 amplitude (in microvolts [μV]) for patients and controls at frontal, central, and parietal sites over the left hemisphere (LH) and right hemisphere (RH) for dot stimuli in the left visual field (LVF) or right visual field (RVF).

region for stimuli in the contralateral right visual field, whereas this contralateral advantage was less evident in patients, Group × Hemisphere interaction: $F(1, 54) = 5.92$, $p < .05$. As a result, the largest difference in N1 amplitude between groups occurred over the left parietal region for stimuli in the right visual field.

N2 amplitude. The amplitude of N2 was markedly smaller in patients than in controls, $F(1, 54) = 38.90$, $p < .0001$. This group difference was greater at medial than lateral sites and at more posterior than anterior sites (see Figures 1 and 2), which was reflected in a Group × Frontal-Parietal × Medial-Lateral interaction, $F(2, 108) = 7.79$, $p < .01$, $\epsilon = .76$. As was seen for N1, there was also a Group × Hemisphere × Visual Field × Frontal-Parietal interaction, $F(2, 108) = 3.85$, $p < .05$, $\epsilon = .72$. This interaction was not, however, significant in an ANOVA of PCA factor scores corresponding to N2, which suggests that it may represent overlapping effects of N1 on amplitude measures in the N2 window.

P3 and slow wave amplitude. Patients had larger P3 amplitude than controls over left and right hemisphere sites, $F(1, 54) = 4.54$, $p < .05$. This group difference was greatest at lateral-parietal sites (see Figures 1 and 2), which was reflected in a Group × Frontal-Parietal × Medial-Lateral interaction, $F(2, 108) = 4.11$, $p < .05$, $\epsilon = .75$. However, an ANOVA of the PCA factor scores corresponding to P3 did not confirm the group main effect, and the Group × Frontal-Parietal × Medial-Lateral interaction only approached significance, $F(1, 108) = 2.83$, $p < .10$. No significant group difference was found for the late positive slow wave potential.

N2–P3 difference. The difference between the N2 and P3 amplitude was computed and submitted to the same ANOVA used for the individual components. As can be seen in Figures 1 and 2, the N2–P3 difference was consistently smaller in patients than in controls, $F(1, 54) = 7.97$, $p < .01$. This group difference in N2–P3 was larger at parietal than frontal sites, Group × Frontal-Parietal interaction, $F(2, 108) = 4.62$, $p < .05$, $\epsilon = .59$, and at medial than lateral sites, Group × Medial-Lateral interaction, $F(1, 54) = 9.14$, $p < .01$. There was also a Group × Hemisphere × Visual Field interaction, $F(1, 54) = 9.30$, $p < .01$. Analyses of simple effects indicated that there was a significant Group × Hemisphere interaction for right visual field stimuli, $F(1, 54) = 4.39$, $p < .05$, but not for left visual field stimuli, $F(1, 54) = 0.28$, $p = .60$. The N2–P3 difference in controls was greater over the left than right hemisphere for stimuli in the right visual field (left $M = 5.33$; right $M = 4.89$), whereas patients tended to show the opposite hemispheric asymmetry for this visual field (left $M = 2.95$; right $M = 3.25$).

Correlational Analyses

The relationship between dot enumeration accuracy and ERP component amplitudes at the midline-parietal site (Pz) was ex-

amined separately for patients and controls. For patients, accuracy of dot enumeration was not significantly related to amplitude of the early ERPs P1 (r = .36, *ns*) or N1 (r = .18, *ns*) potentials. As can be seen in Figure 5, amplitude of N2, P3, and slow wave were significantly related to accuracy in patients. Higher dot enumeration accuracy in patients was associated with greater ERP positivity. This relationship was particularly strong for P3 (r = .78, $p < .001$). The similar positive correlation for N2 (r = .51, $p < .01$) could be due, in part, to overlapping positivity from P3. In contrast, these correlations were not evident for controls ($r = -.26$ to .23, *ns*). There was also a positive correlation between N2–P3 differences and accuracy scores for patients (r = .62, $p < .01$) but not for controls (r = .00, *ns*). The open circles in Figure 5 show the data for the 3 patients who were off medication during testing. Their ERP data are in good agreement with those for the remaining patients who were on antipsychotic medications. Most notably, these unmedicated patients showed no evidence of negativity in the N2 region.

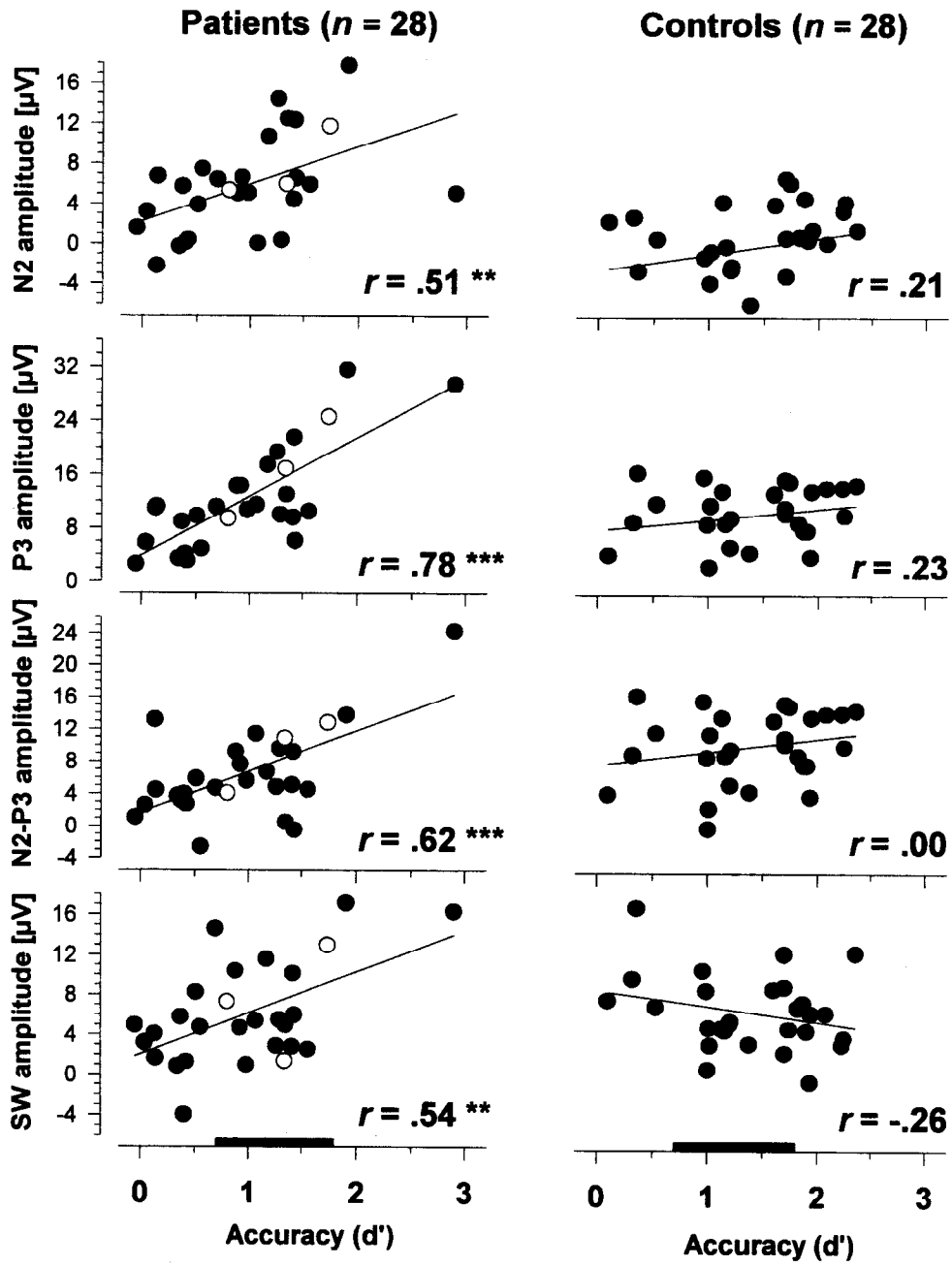

Figure 5. Scattergrams illustrating correlations between dot enumeration accuracy and amplitude (in microvolts [μV]) of N2, P3, N2–P3, and slow wave (SW) at the midline-parietal site (Pz). Data for 3 unmedicated patients are indicated with open circles. $^{**}p < .01$. $^{***}p < .001$.

Correlations were also computed to examine the relation of ERP amplitudes at Pz to symptom ratings. No significant correlations were found between ERP amplitudes and the total positive symptom, negative symptom, or general psychopathology scores on the PANSS or the total BPRS scores. Nor were the ERP amplitudes or dot enumeration accuracy of patients significantly correlated with education level or age. ERP amplitudes of controls were also not significantly correlated with education level or age. Accuracy of dot enumeration among controls was inversely correlated with age ($r = -.51, p < .01$) but not with education level.

Subgroups Matched for Performance Level

Since N2 and P3 amplitude were related to accuracy of dot enumeration, the question arises as to whether the differences between patients and controls on these measures would persist in subgroups of patients and controls with comparable performance levels. There were 15 patients and 15 controls whose accuracy scores (d') were between 0.7 and 1.8, which is indicated by the black bar on the accuracy axis in Figure 5. The mean accuracy of these patients, $d' = 1.24$; $SD = 0.27$, did not differ from that of the controls, $d' = 1.30$, $SD = 0.30$, $t(28) = 0.56$, $p = .58$. The average ERP waveforms for these subgroups were virtually identical to those for the full samples, with patients showing smaller N1 and N2 but greater P3 when compared with controls. There were significant differences between these matched patient and control subgroups in amplitude of N1, $F(1, 28) = 22.79$, $p = .0001$; N2, $F(1, 28) = 52.34$, $p < .0001$; P3, $F(1, 28) = 12.02$, $p < .005$; and N2–P3, $F(1, 28) = 5.64$, $p < .05$. Thus, the subsamples of patients and controls with equivalent accuracy levels showed the same group differences in N1, N2, P3, and N2–P3 as seen for the full samples.

Discussion

Schizophrenic patients were poorer in dot enumeration when compared with controls, which is consistent with prior reports of deficits in visuospatial discrimination and perceptual organization in schizophrenia (O'Donnell et al., 1996; Place & Gilmore, 1980; Rabinowicz et al., 1996). The most striking difference in the visual ERPs of these patients was the marked reduction of their early negative potentials. Although the amplitude of the sensory P1 potential in patients was quite comparable to controls, patient ERP waveforms diverged during the time course of the N1 potential and reached a maximum deviation at about 275 ms after stimulus onset at the peak of the N2 potential. The time frame (100–200 ms) and scalp topography (maximum at lateral parietal sites) of the N1 reduction in schizophrenic patients are consistent with a deficit in early visuospatial attention (Early et al., 1994; Posner et al., 1988). The further reduction of negativity in the N2 region, along with the attenuation of the N2–P3 difference, suggests an additional deficiency of visuospatial processing in schizophrenic patients. Unlike N1, the N2 and N2–P3 reductions in patients had a more medial scalp distribution and were strongly related to accuracy of performance. Although the nature of the cognitive deficit underlying the N2 reduction in schizophrenia needs further study, one possibility is that schizophrenic patients differed in their allocation of conceptual resources to compare the perceptual representation of the central digit and lateral dot stimuli (Giese-Davis et al., 1993). For instance, the larger N2 in controls may indicate greater success in the use of pattern recognition and stimulus comparison processes, whereas patients may rely on more elaborate later cognitive processes reflected by the P3 or slow wave components. It is important to note in this regard that, unlike controls, patients with larger P3 amplitude showed better dot enumeration, suggesting that they were able to use later cognitive processing to compensate for their earlier deficits. If patients and controls did use different cognitive approaches to solve the dot enumeration task, this could also account for why patients with the same accuracy of dot enumeration as controls nonetheless had markedly reduced early ERP negatives.

P1 Component

Evidence from direct recordings in nonhuman primates indicates that the occipital P1 of the visual ERP arises largely from the early activation of modality-specific visual cortex (Schroeder et al., 1995). The possibility that schizophrenia may involve a deficit in early (preattentive) visual processing is suggested by evidence of increased neuronal density in the occipital cortex of schizophrenic patients (Selemon, Rajkowska, & Goldman-Rakic, 1995). The normal P1 amplitude of schizophrenic patients indicates that their poor dot enumeration is not likely to be due to early sensory registration. The P1 component in schizophrenic patients was also similar to that in controls in showing greater amplitude over the right than left hemisphere. Strandburg et al. (1994) similarly found no reduction in the P1 amplitude of schizophrenic patients and also noted greater P1 amplitude over the right than left occipital sites. The P1 asymmetry of patients in the present study was, however, smaller than that found for controls, particularly over parietal and occipital sites where P1 is most evident. The origins of this difference in P1 asymmetry is unknown, and its relation to early sensory or attention processing will need further study.

N1 Component

The influence of selective attention on the N1 potential has been well established. Directing attention to visual stimuli results in an enhancement of N1 amplitude (Clark & Hillyard, 1996; Mangun, 1995; Näätänen & Picton, 1987). In the absence of a defect in early sensory processing, the smaller N1 amplitude in schizophrenic patients may involve a deficit in directing attention to the central digit and dot stimuli in the right or left visual field. This interpretation is consistent with evidence of reduced attention-related negativity in schizophrenia during auditory selective attention tasks (Baribeau-Braun, Picton, & Gosselin, 1983; Michie, Fox, Ward, Catts, & McConaghy, 1990).

The topography of the N1 reduction in patients, with a maximum over left lateral-parietal sites for right visual field stimuli, provides some support for the hypothesis of left hemisphere mediation of visuospatial attentional deficits in schizophrenia (Early et al., 1994; Posner et al., 1988). Posner et al. (1988) observed that schizophrenic patients were slower in reacting to targets in the right than left visual field when attention was not

initially directed to that visual field. This deficit was similar to that seen in patients with left parietal lesions and was hypothesized to stem from an abnormality in a network that controls spatial attention involving anterior language centers and the posterior parietal lobe. Using Posner's paradigm, Carter et al. (1992) found longer reaction times to right than to left visual field stimuli in schizophrenic patients but not in controls. Tomer and Flor-Henry (1989) observed evidence of right hemispatial neglect in unmedicated schizophrenic patients performing letter and form cancellation tests, but O'Carroll et al. (1995) were not able to replicate the latter finding. Although the present study found no evidence of right hemifield neglect in the behavioral performance of patients, the N1 reduction in patients was greatest over left parietal sites for right visual field stimuli. Given the contralateral enhancement of attention-related negativity observed in healthy adults (Clark & Hillyard, 1996; Mangun, 1995), the N1 data for schizophrenic patients do provide partial support for the hypothesized left-sided dysfunction of a neural network mediating visuospatial attention (Posner et al., 1988).

N2 Component

The reduction in ERP negativity in schizophrenia during the dot enumeration test was particularly large at the peak of the N2 potential. Studies using simple visual discrimination tasks (Egan et al., 1994; Ford et al., 1994; Matsuoka et al., 1996) have likewise found smaller N2 amplitude in schizophrenia. Also, the time of maximum difference in ERP negativity between patients and controls in the dot enumeration task (250–300 ms after stimulus onset) corresponds to the time interval where schizophrenic patients showed reduced negativity in the span-of-apprehension task (Strandburg et al., 1994). Reduced negativity in the N2 region is therefore a highly robust abnormality in schizophrenia that is present in a variety of visual tasks. What common mechanisms might account for this N2 reduction in tasks with such different cognitive demands? One possibility is that reduced attention-related processing negativity in schizophrenia begins in the region of N1 and extends into the N2 region. However, the reduction of negativity at N2 differed from that at N1 in its greater magnitude and its medial scalp distribution in contrast to the lateral-parietal maximum of N1 differences.

Giese-Davis et al. (1993) have suggested that the classical N2 potential (also referred to as N2b) reflects the allocation of conceptual resources to process the perceptual representation of stimuli, corresponding to Stage 2 processing in Knight's model of visual information processing. Knight (1984, 1992) reviewed converging evidence that early visual sensory processing, that is, Stage 1 processing, is intact in schizophrenia and that a deficiency in Stage 2 processing is most likely to explain the visual information-processing deficits in schizophrenia. Similarly, Strandburg et al. (1994) postulated that the reduction of span negativity in schizophrenia reflects an impairment in allocating resources to comparison processes during the scanning of the visual icon. In the span-of-apprehension task, stimuli in a 12-letter visual array must be compared with a memory trace of the target stimuli (letters *T* and *F*). The comparison processes in the dot enumeration task are different, in that a central digit must be compared with an estimate of number of dots in the lateral field. However, a common element, which may contribute to the reduced N2 in schizophrenia during these different visual tasks, is the allocation of resources needed for comparison processes involved in initially categorizing stimuli as either matching or not.

A reduction of N2 amplitude in schizophrenia has also been found in the auditory modality (Egan et al., 1994; Ford et al., 1994; O'Donnell et al., 1993; Salisbury et al., 1994). Because the topography of N2 is modality specific, it has been suggested that visual and auditory N2 are generated by different structures of the brain (O'Donnell et al., 1993; Simson, Vaughan, & Ritter, 1977). However, Egan et al. (1994) reported a correspondence between smaller left hippocampal area and reduced N2 amplitude in schizophrenia for both auditory and visual tasks, which suggests that N2 abnormalities in the auditory and visual modality may have a common link.

Late Positive P3 Component

Despite the abundance of evidence of reduced auditory P3 in schizophrenia (Egan et al., 1994; Ford et al., 1994; McCarley et al., 1993; Roth et al., 1986), studies using simple visual discrimination tasks have not consistently found a difference in P3 amplitude between schizophrenic patients and controls (Brecher et al., 1987; Egan et al., 1994; Ford et al., 1994; Matsuoka et al., 1996). In the span-of-apprehension test, Strandburg et al. (1994) found a larger late positive peak at about 400 ms in schizophrenic patients than in controls, but the group difference was significant only at frontal sites. In the present study, P3 amplitude of schizophrenic patients during a cognitively demanding visuospatial task was equal to or greater than that of controls. The apparent enhancement of P3 in patients when compared with controls at lateral sites could stem, at least in part, from an extension of their reduced negativity into the P3 region, which is supported by the lack of a group difference in PCA factor scores corresponding to P3.

Greater late ERP positivity, particularly in the P3 region, was strongly associated with better accuracy of dot enumeration among patients but not controls. This relationship suggests that larger P3 amplitude in patients may reflect greater use of later cognitive processes to compensate for an earlier deficiency in allocation of attentional or conceptual resources. P3 is thought to be related to elaborative cognitive processes, such as stimulus evaluation, and there is evidence that P3 amplitude reflects the amount of cognitive effort or resources devoted to the task (Donchin & Coles, 1988). Thus, those patients who devoted more late cognitive resources to performing the dot enumeration task are likely to have both greater P3 amplitude and better accuracy of performance. The poorer overall accuracy of patients when compared with controls indicates the limitations of using late cognitive processes to overcome early attentional deficits.

N2–P3 Difference

The question arises as to whether the difference between patients and controls in N2 and P3 amplitudes might reflect the contribution of an overlapping slow negative potential, such as contingent negative variation (CNV). If the CNV were smaller

in schizophrenic patients than in controls (e.g., see Pritchard, 1986), this could result in less negativity in the N2 region and greater positivity in the P3 region in patients when compared with controls. Because an overlapping negative slow potential, such as CNV, might be expected to have a similar effect on N2 and P3, the difference between N2 and P3 should be relatively unaffected by it.

The N2–P3 difference was consistently smaller in patients than controls, with the largest difference at medial-parietal sites. Moreover, the N2–P3 difference in controls was greater over left than right hemisphere sites to stimuli in the right but not left visual field, whereas patients did not show this asymmetry pattern. These group differences are in accordance with those described for N2, which suggests that they were not due to an overlapping negative slow potential, such as CNV. It should also be noted that no reaction time response was used in the dot enumeration task, and that responses were specifically delayed until after the recording epoch to reduce the influence of overlapping response-related potentials. In contrast, Strandburg et al. (1994) preceded the visual letter array in the span-of-apprehension task with a warning tone and thereby elicited an identifiable CNV, but they found no evidence of a reduced CNV in schizophrenic patients.

Medication Issue

Another important question is whether the reduced N1 or N2 amplitude in schizophrenia, or their lack of a P3 reduction, could be due to effects of antipsychotic medication. Ford et al. (1994) measured auditory and visual ERPs of unmedicated schizophrenic patients who were retested after 4 weeks of antipsychotic treatment. There was no significant change in N1, N2, or P3 amplitudes. There have, however, been reports that clinical improvement during neuroleptic treatment is accompanied by an increase in P3 amplitude to visual stimuli (Duncan et al., 1987), but this may not be sufficient to normalize the P3 amplitude of schizophrenic patients (e.g., Mintz et al., 1995). Thus, there is no evidence that antipsychotics could produce the marked reductions of N1 or N2 observed for patients in the present study. Although P3 amplitude may increase during antipsychotic treatment, it is unlikely that this could account for the even greater visual P3 amplitude of schizophrenic patients when compared with controls. Also, the ERP data for 3 unmedicated patients showed essentially no evidence of N2 but large P3 amplitude (Figure 5). Further study is, however, needed to determine whether treatment with typical or atypical neuroleptics is associated with any change in ERP indices of visuospatial attention in schizophrenia.

Conclusions

The schizophrenic patients demonstrated the same ERP component structure as normal adults. This is important because it suggests that patients and controls used the same stages of information processing during the dot enumeration task. The main abnormality in patients was the profound reduction of early negative components that are known to reflect selective attention and allocation of conceptual resources. The reduction of N1 and N2 amplitude in schizophrenia is not likely to result from a generalized performance deficit, such as might result from a failure to attend to the task or lack of motivation or effort. Even patients whose accuracy of dot enumeration was the same as controls showed markedly reduced N1 and N2 amplitude. Also, the large P3 characteristic of patients indicates that they were devoting considerable effort and resources to performing the task. Rather, the reduction of N1 and N2 amplitude in schizophrenia appears to represent a basic deficit in early visuospatial processing, which can be overcome, at least partially, by enhanced later cognitive processing. These findings support the hypothesis that deficits in visual information processing in schizophrenia occur in the first 100–300 ms following stimulus onset (Strandburg et al., 1994).

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