High-Density Recording and Topographic Analysis of the Auditory Oddball Event-Related Potential in Patients with Schizophrenia

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Background: Prior research has shown reductions of the N1, N2, and P300 auditory event-related potential (ERP) components in schizophrenic patients. Most studies have shown a greater P300 reduction in left versus right temporal leads in schizophrenic patients. These studies were done with sparse electrode arrays, covering restricted areas of the head, thus providing an incomplete representation of the topographic field distribution.

Methods: We used a 64-channel montage to acquire auditory oddball ERPs from 24 schizophrenic patients and 24 control subjects. The N1, P2, N2, P300, and N2 difference (N2d) amplitudes and latencies were tested for group and laterality differences. Component topographies were mapped onto a three-dimensional head model to display the group differences.

Results: The schizophrenic group showed reduction of the N1 component, perhaps reflecting reduced arousal or vigilance, but no N1 topographic difference. An N2d was not apparent in the schizophrenic patients, perhaps reflecting severe disruption in neural systems of stimulus categorization. In the patients, the P300 was smaller over the left temporal lobe sites than the right.

Conclusions: The increased ERP spatial sampling allowed a more complete representation of the dipolar nature of the P300, which showed field contours consistent with neural sources in the posterior superior temporal plane. Biol Psychiatry 1998;44:982–989 © 1998 Society of Biological Psychiatry

Key Words: P300, N1, N2, schizophrenia, event-related potentials, 64-channel montage

Introduction

Between 300 and 400 msec after the presentation of a stimulus there is a large deflection in the event-related potential (ERP), the P300 (Sutton et al 1965). The P300 can be elicited using an auditory oddball paradigm in which infrequent “oddball” target tones are interspersed into a stream of frequent “standard” tones, and the subject is instructed to make some response to, usually to count silently, the oddball targets. The P300 is sensitive to the subjective frequency of a stimulus (Ritter et al 1968) and to its task relevance (Courchesne et al 1975; Donchin 1979). The P300 has been proposed as an index of multiple cognitive processes, including context updating, memory consolidation, orienting, processing termination, and decision making (reviewed in Donchin and Coles 1988; Johnson 1988; Verleger 1988). The P300 is not a single phenomenon, but is comprised of subcomponents supported by separate neural substrates (Johnson 1988, 1993; Ruchkin et al 1990). Some of the neural structures that have been associated with the P300 are the medial temporal lobe including hippocampus (Neshige and Luders 1992; O’Donnell et al 1993; Tarkka et al 1995), frontal cortex (Neshige and Luders 1992), the temporal parietal junction (Knight et al 1989), and auditory cortex in the superior temporal lobes, including the posterior superior temporal gyrus (STG; Knight et al 1989; Lovrich et al 1988; Tarkka et al 1995). These P300 neural substrates have been described using topographic voltage mapping (Giard et al 1988; Lovrich et al 1988), current density mapping (Law et al 1993), and dipole modeling (O’Donnell et al 1993; Tarkka et al 1995), and through comparison with other methodologies, including magnetoencephalography (Rogers et al 1991; Tarkka et al 1995) and intracranial recording (Neshige and Luders 1992).

There is a well-established finding of reduced P300 amplitude in schizophrenia (reviewed in Bruder et al 1996; McCarley et al 1997; Roth et al 1986). Many studies have found that this P300 amplitude reduction is not uniformly distributed across the scalp, but that the amplitude reduc-
tion is greater at electrodes over the left temporal region than the right temporal region (e.g., Faux et al 1993; McCarley et al 1991; Morstyn et al 1983; Salisbury et al 1998; Turetsky et al 1988; but see also Ford et al 1994a; Pfefferbaum et al 1989; reviews in Bruder et al 1996; McCarley et al 1997). It has been suggested that differences in task demands may account for some studies not replicating the P300 lateralization; studies that find lateralization use a silent count task, whereas studies that do not find lateralization use a motor (key press) response (Bruder et al 1996). The left lateralized reduction has also been found in unmedicated schizophrenics (Faux et al 1993) and in first-episode schizophrenics (Salisbury et al 1998), implying that the asymmetry reflects an aspect of the disease process rather than an effect of medication. Interestingly, the asymmetry is reversed in left-handed schizophrenics, i.e., the amplitude reduction is largest over the right hemisphere for the left-handed patients (Holinger et al 1992). The electrophysiological asymmetry has been related to brain structure using magnetic resonance imaging. In a study comparing the volume of temporal lobe structures with P300 amplitude, McCarley et al (1993) found that, for schizophrenic subjects, the auditory P300 amplitude reduction over left temporal lobe sites was correlated to the reduction in volume of the left posterior STG, one of the probable auditory P300 generators.

Although the P300 has received the most attention, it is not the only auditory ERP component that is affected by schizophrenia. Amplitude and latency alterations have also been reported for the N1 (Ford et al 1994b; Kessler and Steinberg 1989; O’Donnell et al 1994), the P2 (O’Donnell et al 1994; Sandman et al 1987), the N2 (Ford et al 1994b; Javitt et al 1995; O’Donnell et al 1993, 1994; Sandman et al 1987), and, in the target minus standard difference wave, the mismatch negativity (Javitt et al 1995) and the N2 difference (N2d) (O’Donnell et al 1993). These components are thought to arise from a combination of neural sources in primary and secondary auditory cortical areas in the superior and lateral temporal lobes, with contributions from frontal lobe activity (Giard et al 1988, 1994; Hegerl et al 1994; Pantev et al 1995; Ponton et al 1993; Rogers et al 1991; Tarkka et al 1995).

The ability to relate scalp-recorded electrical signals to underlying neural activity depends, in part, on a full and accurate description of those electrical signals. The actual linking of scalp recordings to neural generators requires solving a formal inverse problem; however, this inverse problem is “ill-posed,” that is, it does not have an unique solution and small errors in the input data can result in unconstrained errors in the solution. If an ERP recording system has only a few electrodes, clustered over a limited scalp area, then there are large gaps between the electrodes, and some spatial characteristics of the ERP may not be fully described (Tucker et al 1994; Wikswo et al 1993). If the spatial sampling is sparse, then there can be spatial aliasing of the signal (Srinivasan et al in press). Thus if undersampled ERP data were entered into an inverse formulation, there could be large and unpredictable errors in the resulting solution. It has been demonstrated that nonredundant spatial information can be derived from recording systems with more than 100 electrodes (Gevins et al 1991), and the limit at which unique information is present at each electrode may be between 200 and 300 electrodes (Srinivasan et al 1998). Recently there have been several published studies that have provided detailed descriptions of the scalp topography of the ERP using dense arrays (64 or more electrodes) including studies of semantic priming (Curran et al 1993), working memory (Gevins et al 1996), visual attention (Potts et al 1996), and auditory attention (Potts et al 1998); however, to our knowledge, all prior ERP studies in schizophrenia have been done with low-density recording arrays (32 or fewer electrodes, sometimes as few as four midline electrodes), with little or no coverage of inferior scalp sites, thus the topographic distribution of the scalp-recorded electrical field has been incompletely characterized and perhaps distorted.

In this study we examined the field distribution of the auditory oddball ERP in a group of patients with schizophrenia and group of control subjects, demonstrating the ability to perform high-density ERP recording in schizophrenic patients. The P300 was analyzed for lateral asymmetry over the temporal scalp leads with the specific hypothesis of a group by side interaction showing the temporal region target P300 smaller on the left side than on the right side in the schizophrenic group, whereas the control group would not show this asymmetry. Since abnormalities have been reported in other long-latency ERP components in schizophrenia, including the N1, P2, N2, and N2d, these components were subjected to an exploratory analysis.

Methods and Materials

Subjects

The patient group (n = 24) was recruited from outpatient treatment and inpatient wards at the Brockton Veterans Affairs Medical Center, Brockton, Massachusetts. Diagnoses were made from the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al 1990a). The patient group included 11 of undifferentiated type, 10 paranoid, 1 disorganized, and 1 catatonic schizophrenic patients; subtype data was unavailable for 1 patient. Subjects were right-handed men between the ages of 26 and 55 years, had no history of electroconvulsive shock treatment or neurological illness, no alcohol or drug abuse in the last 5 years or lifetime history of drug or alcohol addiction (DSM-III-R criteria), no alcohol use 24 hours prior to testing, and the ability
and desire to participate as evidenced by giving informed consent. Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987; general mean = 33.5, SD = 9.23; positive scale mean = 17.64, SD = 5.98; negative scale mean = 17.86, SD = 5.34; data missing for 2 subjects). Mean age of disease onset was 21.8 years (SD = 3.16) and mean duration of illness was 21.5 years (SD = 6.52). Twelve subjects were on conventional neuroleptic medications, 5 were on atypical neuroleptics, 1 was on a combination of conventional and atypical medications (mean chlorpromazine equivalent 668 mg, SD = 394), 2 patients were unmedicated at time of testing, and data were unavailable for 4 subjects. Control subjects (n = 24) were recruited by newspaper advertisement. The same exclusion criteria were applied to the controls as to the patients with the addition of no lifetime history of mental illness (SCIO-NP, Spitzer et al. 1996). The control group was chosen to be similar in age (control: mean = 39 years, SD = 8.9; schizophrenic: mean = 43 years, SD = 9.7; p = .09) and parental socioeconomic status (SES; control: mean = 2.7, SD = 0.98; schizophrenic: mean = 3.1, SD = 0.73; p = .24) to the patient group; parental SES data were unavailable for 6 of the patients.

**Stimuli and Tasks**

Stimuli were high (1.5 kHz, 97 dB SPL) and low (1.0 kHz, 97 dB SPL) tones of 40-msec duration (10-msec rise time) presented pseudorandomly with interstimulus intervals varied between 1.0 and 1.4 sec (1.2-sec mean) through ETYMOTIC insert headphones (Etymotic Research, Elk Grove Village, IL) over a continuous 70-dB binaural white noise background. The low tones were designated as Standards and presented on 85% of the trials; the high tones were designated as Targets and presented on 15% of the trials. There were 600 trials presented in blocks of 100. Subjects were instructed to silently count the number of high tones presented, resetting their count at the breaks every 100 trials.

**Data Collection and Preprocessing**

Raw electroencephalographic (EEG) data were collected at 250 samples per second, referenced to the vertex, using two linked 32-channel Neuroscan Synamps (Neuroscan Inc, Herndon, VA) and a 64-channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Epochs were 700 msec, in length with a 100-msec prestimulus baseline. The raw EEG data were passed through a computerized artifact detection algorithm and trials with out of range data (±75 μV) were excluded from further analysis. The data were digitally low-pass filtered at 30 Hz to eliminate residual electrical noise. The EEGs were averaged by stimulus type (Standard, Target) to create the ERP waveforms. The data were transformed into an average reference representation to attenuate spatial distortions due to choice of reference sensor (Bertrand et al. 1985; Dien 1998; Tucker et al. 1994). Grand average waveforms were created by averaging together the individual subject averages for each group (Schizophrenic, Control) and stimulus type. Since some characteristics of the ERP are only apparent in the target minus standard difference wave, such a difference waveform was created for each subject group.

**Results**

Figure 1 shows the electrode locations in the 64-channel net with 10/20 system sites included for reference. To show the analysis windows, a single channel of data (the vertex) is shown in Figure 2 with the analysis windows delineated.

**A Priori Hypothesis Test**

For the target P300 in the temporal scalp region leads there was a Group × Side interaction, F(1.46) = 4.281, p < .05, showing a left side reduction in the schizophrenic group. The higher-order interaction with electrode site was not
significant. Subsequent t tests comparing the mean amplitude of the four left temporal electrodes to the four right temporal electrodes in the two groups showed that the left side was significantly smaller than the right in the patient group (p < .05), but there was no such difference in the control group. Figure 3 shows the waveform plots from electrodes 16 and 45, the electrodes closest to T3 and T4 in the sensor net, showing the left side P300 reduction in the patient group. The topographic map in Figure 4 shows the superior posterior positive voltage and anterior inferior negative dipolar voltage distribution of the P300 and the left side P300 amplitude reduction in the schizophrenic group over the left temporal region. There was no Group × Side interaction in the temporal scalp region leads for the other components.

**Exploratory Analyses**

In the exploratory analyses, for the N1 there was an effect for Group, F(1,46) = 18.068, p < .0001, with the mean amplitude less negative for the schizophrenic group than for the controls. There was a main effect for Site, F(8,368) = 95.037, p < .0001 and Site interacted with Stimulus, F(8,368) = 4.932, p < .01.

For the P2 there was a Stimulus by Group interaction, F(1,46) = 10.177, p < .01, showing that the P2 was less positive to the target stimuli in the control group only. There was also an effect for Site, F(8,368) = 11.961, p < .0001.

For the N2 there was an effect for Stimulus, F(1,46) = 19.770, p < .0001, showing more negativity to the target stimuli. The Stimulus effect interacted with Group, F(1,46) = 12.301, p < .001, showing more negativity to the target stimuli in the control group only. There was an effect for Site, F(8,368) = 7.237, p < .01, and the Site effect interacted with Stimulus, F(8,368) = 11.670, p < .0001, and Side, F(8,46) = 4.273, p < .001.

For the P300 there was an effect for Group, F(1,46) = 9.693, p < .01, showing a reduced P300 amplitude in the schizophrenic group, and there was an effect for Stimulus, F(1,46) = 96.778, p < .0001, showing an increased P300 amplitude to the target stimuli. The Group and Stimulus effects interacted, F(1,46) = 10.634, p < .005, indicating that the P300 enhancement to the targets was smaller in the patient group. There was an effect for Site, F(8,368) = 28.783, p < .0001, and the Site and Stimulus effects interacted, F(8,368) = 3.127, p < .0001.

In the difference wave the N2d was less negative in the schizophrenic group, F(1,46) = 15.616, p < .0005. There was also an effect for Site, F(8,368) = 8.931, p < .0001. Figure 5 is the topographic map of the N2d field illustrating the apparent absence of the N2d in the patient group.

In the latency analysis, the N2 and P3 showed a main
Discussion

Like most prior auditory P300 studies in schizophrenia, these data showed a P300 reduction in the schizophrenic group. This study also found a specific left temporal scalp region reduction of the P300 in the schizophrenic group. The P300 is known to have multiple generators, and one P300 generator is thought to lie in the posterior STG (Knight et al 1989; Lovrich et al 1988; Tarkka et al 1995). A study by McCarley et al (1993) showed correlation between left temporal P300 amplitude reduction and left posterior superior temporal gyrus volume reduction in schizophrenia. The P300 here was reduced in amplitude in the left temporal leads in the patient group, consistent with reduction in the amplitude of a temporal lobe P300 generator in the schizophrenic subjects.

The schizophrenic patients in this study also showed an N1 amplitude reduction, although there was no N1 topographic difference between the groups. The N1 is thought to be generated in primary and secondary auditory areas in superior and lateral temporal cortex (Giard et al 1988; Hegerl et al 1994; Pantone et al 1993; Ponton et al 1993; Rogers et al 1991; Tarkka et al 1995) with a possible frontal lobe contribution (Giard et al 1994). The N1 was not sensitive to task demands here, i.e., it did not vary by stimulus type. The N1 can be enhanced to relatively infrequent stimuli in some paradigms, and this enhancement has been attributed to the presence of an underlying component, the mismatch negativity (MMN), which is coincident to, but distinct from, the N1 (reviewed in Näätänen 1990 and 1992). The N1 can also be enhanced by motivation (Wilkinson and Morlock 1966) and alertness (Fruhstorfer and Bergstrom 1969), both of which may be reduced in schizophrenic patients. Since the N1 reduction in the schizophrenic group was neither task specific nor topographically distinct, the reduction could represent either a general early auditory processing deficit or reduced arousal, vigilance, or motivation in the schizophrenic subjects.

In contrast, the P2 was larger in the schizophrenic group than in the controls to the target stimuli only, whereas the N2 was smaller. Actually, the field polarity of both the P2 and the N2 at the superior sites used in the ANOVA was positive in the average reference, and the voltage was less positive to the targets for the controls only, suggesting a single effect spanning both component windows. An inspection of the
target minus standard difference wave supports this interpretation. For the controls, the vertex difference wave shows two voltage deflections, a positive deflection coincident with the P300 and an earlier negative deflection coincident with both the P2 and N2, referred to here as the N2d after O’Donnell et al (1993). The schizophrenic group does not show any evidence of an N2d (Figure 4). This is consistent with O’Donnell et al (1993), who found an N2 reduction in schizophrenia and an even larger reduction of the difference N2d. The N2 is thought to index stimulus classification (e.g., target vs. nontarget; Simson et al 1976, 1977a, 1977b), and its reduction or absence in schizophrenia has been interpreted as indicating a disruption of neural systems of attention (Salisbury et al 1995). Consistent with that interpretation, the N2d here was sensitive to task demand, occurring only to target stimuli (but only for the control subjects). The topography of the N2d, as shown in the three-dimensional maps in Figure 5, shows an anterior distribution, with negativity over superior central sites and positivity over inferior frontal sites. The N2 is generally thought to arise from neural sources in the superior and medial temporal lobes (Simson et al 1977a, O’Donnell et al 1993), and N2d reduction in schizophrenia has been correlated with temporal lobe volume reductions (O’Donnell et al 1993); however, recent high-density ERP studies of both the visual and auditory N2d in normal subjects have suggested that the N2d, like the N1, may have a distinct frontal contribution (Potts et al 1996; 1998). Some areas of frontal cortex are thought to be involved with selective attention (Posner and Petersen 1990) and working memory (Goldman-Rakic 1988). Patients with schizophrenia show disruptions of attention (reviewed by Baff 1993; Nestor and O’Donnell 1998) and working memory (Goldman-Rakic 1991; Park and Holzman 1992), and frontal lobe dysfunction in schizophrenia is frequently described in hemodynamic neuroimaging studies (reviewed by Andreasen et al 1992; Gur and Pearlson 1993).

Using recent advances in high-density ERP recording and topographic mapping, this study provided support for the hypothesis of reduction in strength of a left temporal lobe P300 generator in schizophrenia. We also found evidence in the diminished or absent N2d of disruption in attention networks in schizophrenia. Thus the application
of technical improvements in ERP acquisition and analysis to the study of psychopathology has provided a stronger link between observed scalp electrical field abnormalities, disturbed cognitive systems, and underlying neural dysfunctions in schizophrenia.

This project was supported by grant MH40799-09 from the National Institute of Mental Health and by the Veterans Administration through the Research Center for Basic and Clinical Neuroscience of Schizophrenia (RWM).

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