P300 Topography Differs in Schizophrenia and Manic Psychosis

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Background: Overall and left temporal scalp area reductions of P300 have been demonstrated in schizophrenia. P300 amplitude and topography in psychotic affective disorder, a crucial comparison in assessing the specificity of P300 abnormalities to schizophrenia, are not well studied.

Methods: P300 was recorded from 35 schizophrenic, 20 psychotic manic, and 30 control subjects. All were righthanded men.

Results: P300 was reduced in both psychotic groups relative to control subjects. Anteroposterior P300 topography differed between patient groups, with schizophrenic subjects showing posterior reduction and bipolar subjects showing anterior reduction. Schizophrenic subjects showed an abnormal asymmetry, with smaller P300 over the left temporal scalp site than the right. Both bipolar and control subjects showed a left greater than right asymmetry.

Conclusions: Widespread auditory P300 reductions were present in schizophrenia and bipolar disorder with psychosis, but subtle topographic differences were present in the two diseases. Although unequivocal knowledge of neural generators cannot be derived from topography alone, differences in topography imply different generator configurations. Based on previous studies, the posterior P300 reductions in schizophrenia may reflect abnormalities of a generator located in the left superior temporal gyrus. The frontal reductions in bipolar psychosis may reflect abnormalities in a hypothetical frontal generator, consonant with reports of altered frontal lobe function in mania. Biol Psychiatry 1999;45:98–106 © 1999 Society of Biological Psychiatry

Key Words: Bipolar disorder, psychosis, P300, schizophrenia, topography

Introduction

Transmission of information in the nervous system is subserved by electrical impulses between neurons. Thus the brain responses to discrete, repetitive stimuli can be observed in the electroencephalogram (EEG) by averaging multiple trials. These event-related potentials (ERPs) can be either early and sensory in nature, affected by the physical characteristics of the stimuli, or later and cognitive in nature, affected by the subjective cognitive operations of the subject (Donchin 1979; Hillyard et al 1973; Sutton et al 1965). One such long-latency ERP, the P300, appears, for instance, when subjects monitor trains of stimuli for rarely presented targets (oddballs), and is thought to reflect the operations of short-term working memory (Donchin 1981; Donchin and Coles 1988). Due to its indexing of simple cognitive operations, P300 has been widely studied in psychiatric disorders, particularly schizophrenia, as a probe of dysfunction in attention.

Widespread scalp-recorded amplitude reduction of the auditory P300 event-related potential in schizophrenia is well documented and robust (e.g., Roth and Cannon 1972; Begleiter and Porges 1986; Pritchard 1986). Furthermore, auditory P300 reduction in schizophrenia appears to show trait characteristics, being unimproved with resolution of overt psychotic symptomatology (Duncan 1988; Ford et al 1994; Rao et al 1995); even when variation with scores on the Brief Psychosis Rating Scale are reported (Hokama et al personal communication; Maeda et al 1996), P300 amplitudes remain smaller in schizophrenic than in control subjects. In addition to overall P300 voltage reduction, left temporal scalp area reductions of P300 have also been demonstrated, and correlate with severity of positive symptoms and reductions of left posterior temporal gyrus cortical gray matter, a putative P300 generator site (e.g., McCrady et al 1993). This left temporal P300 reduction, reported and replicated by this laboratory in a well-studied inpatient sample of chronically ill schizophrenic subjects (SZ) (e.g., Morstyn et al 1983; Faux et al 1990; Salisbury et al 1994), off-medication SZ (Faux et al 1993), first episode SZ (Salisbury et al 1998), and never-medicated schizotypes (Salisbury et al 1996), remains somewhat controversial. Although it has been replicated by most independent groups (e.g., Strik et al 1993; 1994; Gerez and Tello 1995; Souza et al 1995; Bruder et al 1996; Bolsche et al 1996; Weisbrod et al 1997; Turetsky et al 1998), several others have been unable to replicate this left temporal P300 reduction (Pfefferbaum et al 1989; Ford et al 1994; Stefansson and Jonsdottir 1996).
In chronically ill affective disorder with psychosis, a crucial comparison group for assessing the specificity of P300 abnormalities to schizophrenia, the nature of P300 reductions and topographic asymmetry is not well studied. The presence of P300 amplitude reduction in affective disorder is somewhat equivocal. Some studies have shown reduction in amplitude (e.g., Röschke et al 1996; Gangadhar et al 1993), but others failed to find reduced P300 amplitude (e.g., Bruder et al 1991; Swanwick et al 1996; Hansenne et al 1994, non-suicide attempters; Sara et al 1994). Of particular note are studies that examined P300 in psychotic versus nonpsychotic affective disorder. For example, Muir et al (1991) reported that P300 amplitude was reduced in bipolar psychotic disorder, but not in unipolar depression. Similarly, Santosh et al (1994) reported that P300 was reduced only in those depressed patients with hallucinosis or delusions. Thus, P300 reduction in affective disorder may reflect underlying psychosis in contrast to an underlying abnormal affective process. Finally, these studies are typically restricted to a few midline electrodes, such that P300 scalp topography remains largely unassessed in affective disorder, although Souza et al (1995) reported normal topography of P300 to auditory stimuli in bipolar disorder.

Here we report a study of a new chronically ill sample of 35 right-handed, male, schizophrenic patients, and a new sample of 20 right-handed, male, bipolar manic patients with psychotic features. All patients were acutely psychotic, but not chronically institutionalized. Thirty right-handed, male, psychiatrically normal subjects served as a control group. The aims of this study were to determine the presence or absence of P300 left temporal abnormalities in a new, less ill, sample of schizophrenic subjects, the presence or absence of midline and left temporal abnormalities in a group of affective psychotic subjects, and the presence or absence of P300 topographic differences between these two groups and control subjects.

Methods and Materials

Subjects

Patients were recruited from consecutive admissions to McLean Hospital, and comprised two groups. One group consisted of 35 right-handed, male, schizophrenic patients (average illness duration 12.9 years). The second consisted of 20 right-handed, male, manic patients with psychotic features (average illness duration 7.9 years). Prior to inclusion, subjects were screened for age (18–55 years), IQ above 75, normal hearing, and negative history of seizures, head trauma with loss of consciousness, neurological disorder, and lifetime alcohol or drug dependence. DSM-III-R diagnoses were determined via SCID interview (Spitzer et al 1990). All subjects gave informed consent, and were paid to participate. All subjects performed the Mini-Mental State Examination (Folstein et al 1975) to rule out any dementia or delirium, the information subscale of the WAIS-R (Wechsler 1981) as a gross estimate of preonset intellectual functioning and fund of information, and the Digits forward and backward subscales of the WAIS-R to test immediate/short-term memory, and attention and concentration. In addition, patients’ psychosis was rated via the GAS (Endicott et al 1976), and BPRS (Overall and Gorman 1962). Subject characteristics and test scores are presented in Table 1. All groups were strongly right-handed (Oldfield 1971). Both chronically ill patient samples subjects showed significantly lower socioeconomic status (SES) than control subjects, consistent with lowered social/occupational capacity. The parental SES of schizophrenics was slightly lower than the parental SES of affective psychotic and control subjects, but not significantly so, and all groups were middle class or above. Groups performed nearly identically on the Mini-Mental Status Exam. Compared to control subjects, both patient samples displayed a smaller fund of information, and somewhat impaired attention and concentration. The statistically significant results reported below remained the same when WAIS-R scores were used as covariates.

ERP Recording

Subjects silently counted binaurally presented target tones (97-dB, 1.5-kHz tones, 50-msec duration, 10-msec rise/fall, 15% of trials) among standard tones (97 dB, 1 kHz) against a background of 70-dB white noise. EEG activity was recorded from the scalp through 28 tin electrodes in preconfigured caps (ElectroCap International) using a Neuroscience amplifier/stimulator and Neuroscan software. Electrode sites included all 10/20 sites excluding T1/2, and including Oz; FTC1/2; TCP1/2, PO1/2; and CP1/2. Linked earlobes were used as the reference, the forehead as ground. Two electrodes located medially to the right eye, one above and one below, were used to monitor vertical eye movements. Electrodes placed at the outer canthi of the eyes were used to monitor horizontal eye movements. All electrode impedances were below 3 kΩ, and the ears were matched within 1 kΩ. The EEG amplifier band-pass was 0.15 (6 dB/octave rolloff) to 40 Hz (36 dB/octave rolloff). Single trial epochs were digitized at 3.516 msec/sample. Each epoch was of 900-msec, duration, including a 100-msec, prestimulus baseline. Averaging and artifact rejection were done off-line. ERP responses were convolved with a zero phase-shift digital low-pass filter at 8.5 Hz with a 24-dB/octave rolloff to remove ambient electrical noise, muscle artifact, and alpha contamination. Within each 200-trial block, epochs from each electrode site were baseline corrected by subtraction of the average prestimulus voltage, and corrected for eye movement artifact using regression-based weighting coefficients (Semlitch et al 1986). Subsequently, epochs that contained voltage exceeding ±50 μV at F7, F8, Fp1, or Fp2 were rejected. Next, target trials were examined and rejected if residual horizontal eye movements were present (i.e., asymmetrical, but <50-μV artifact), or if the entire poststimulus epoch did not cross baseline (i.e., was completely negative or positive). Averages were computed for the brain responses to target tones. Peak P300 amplitude, which accounts for individual variations in P300 latency, was measured as the most positive point from 250 to 650
Table 1. Demographic, Neurocognitive, and Clinical Information

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Manic psychosis</th>
<th>Control</th>
<th>Significance (one-way ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>35</td>
<td>20</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.3 ± 7.0</td>
<td>32.0 ± 7.0</td>
<td>35.4 ± 7.4</td>
<td>ns</td>
</tr>
<tr>
<td>Years since onset</td>
<td>12.9 ± 6.7</td>
<td>7.9 ± 6.0</td>
<td></td>
<td>p = .009</td>
</tr>
<tr>
<td>Handedness</td>
<td>0.74 ± 0.19</td>
<td>0.75 ± 0.20</td>
<td>0.85 ± 0.12</td>
<td></td>
</tr>
<tr>
<td>SES</td>
<td>4.1 ± 1.1d,e</td>
<td>3.1 ± 1.4d,j</td>
<td>2.1 ± 1.1d,d</td>
<td></td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.5 ± 1.2</td>
<td>1.8 ± 1.1</td>
<td>1.8 ± 1.1</td>
<td>p = .022</td>
</tr>
<tr>
<td>Mini-Mental</td>
<td>27.1 ± 2.85f</td>
<td>28.2 ± 2.3</td>
<td>29.4 ± 0.9d</td>
<td></td>
</tr>
<tr>
<td>WAIS-R Digits-forward</td>
<td>18.5 ± 5.4d</td>
<td>21.2 ± 4f</td>
<td>25.2 ± 3d,f</td>
<td>p = .001</td>
</tr>
<tr>
<td>WAIS-R Digits-backward</td>
<td>6.7 ± 2.3d</td>
<td>7.9 ± 2.2</td>
<td>9.4 ± 2Ad</td>
<td>p = .001</td>
</tr>
<tr>
<td>GAS</td>
<td>35.8 ± 13.1</td>
<td>34.9 ± 10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>39.9 ± 9.2</td>
<td>36.9 ± 8.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>362.2 ± 288.9</td>
<td>270.75 ± 154.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ns: not significant

*Edinburgh inventory (Oldfield 1971): −1 = left-handed, 1 = right-handed.
*Socioeconomic status (Hollingshead 1965): 5 lowest, 1 highest.
*Indicates schizophrenic and control groups significantly different on post hoc Scheffé tests (p < .05).
*Indicates schizophrenic and affective psychotic groups significantly different on post hoc Scheffé tests (p < .001).
*Indicates no two groups significantly different on post hoc Scheffé tests.
*Summed scores Mini-Mental Status Exam (Folstein et al 1975): score range 0–30.
*Summed raw scores Wechsler Adult Intelligence scales (Wechsler 1981).
*Global assessment scale (Endicott et al 1976).
*Brief Psychiatric Rating Scale (Overall and Gorman 1962).
*Chlorpromazine equivalents.

...msec at each recording site. Peak P300 latency was measured along the sagittal midline (Pz).

**Analyses**

One-way analyses of variance (ANOVA)s with post hoc Scheffé tests were conducted to assess group differences in demographic, clinical, and basic neuropsychological performance. For P300, mixed-model repeated-measures ANOVA was used to test for effects along the sagittal midline and over temporal lobes. Subsequent mixed-model repeated-measures ANOVA pairings each group were conducted in the case of significant group effects and/or group interactions.

**Results**

For target count, all groups were over 90% accurate, but the schizophrenic group’s performance (90.1% accurate) was significantly worse than the control group’s (97.0%; p < .05). The affective group (93.1%) did not differ significantly from either other group. Including accuracy differences as a covariate had no effect on significance levels reported below. The mean number of trials used to construct target averages did not differ significantly between groups, with approximately 16 trials surviving artifact rejection. Although the overall BPRS scores were not significantly different between patient groups, there were qualitative differences in the patterns of scores. A positive factor was constructed using BPRS items also on the positive subscale from the PANSS (Kay et al 1986). This positive factor did not differ significantly between groups. Using the four factors of the BPRS (thinking disturbance, hostile–suspiciousness, withdrawal–retardation, and anxious depression), significant differences were observed for thinking disturbance and withdrawal–retardation, both significantly higher in the schizophrenia group. In comparisons between groups on individual BPRS items, the schizophrenia group showed significantly greater mannerisms and posturing, suspiciousness, hallucinations, and blunted affect, and the bipolar manic psychosis group showed greater grandiosity and excitement.

Rank-order Spearman’s correlations revealed a significant negative correlation between total BPRS score and P300 amplitude at the frontal site (Fz) in the bipolar group (rho = −.49, p = .03). This was largely driven by a significant negative correlation between suspiciousness and P300 amplitude at Fz (rho = −.64, p = .002). There were no significant correlations between BPRS factors or item scores and P300 in the schizophrenia group.

Mean ERP amplitudes and latencies for each group are presented in Table 2. Group grand averaged ERPs to target tones, constructed by averaging of each individual’s waveform, are presented in Figure 1. Overall, both psychotic patient groups showed widespread P300 voltage reductions relative to control subjects. The two patient groups showed roughly equally reduced P300 amplitude over right temporal lobe (T4), but the schizophrenic group was nearly twice as reduced over left temporal lobe (T3) as the...
bipolar group. Furthermore, both groups of patients were reduced along the sagittal midline, but the schizophrenic group showed the smallest posterior amplitudes, and the bipolar group showed the smallest frontal amplitudes.

P300 latency was analyzed along the sagittal midline (Fz, Cz, Pz). P300 latency was significantly different between groups ($F_{2,82} = 3.74, p = .028$), and significantly shorter frontally than posteriorly in all three groups ($F_{2,164} = 6.67, p = .002$). Post hoc analyses revealed that the schizophrenia group was significantly longer ($p < .05$) in P300 latency than control subjects at Fz (407.4 vs. 369.8 msec) and Pz (412.6 vs. 381.6 msec).

The bipolar group did not differ significantly from either other group in P300 latency at any midline site.

Mean peak P300 amplitude at lateral temporal sites for each group are presented in Figure 2. Analysis of lateral temporal amplitudes revealed significant differences between groups ($F_{2,82} = 9.87, p < .001$). In addition, there was a significant group by side interaction ($F_{2,82} = 5.14, p = .008$). Comparison of the schizophrenic and control groups showed that schizophrenics were smaller than control subjects at lateral temporal sites ($F_{1,63} = 21.19, p < .001$), and that groups showed opposite lateral temporal topography (main effect of side: $F_{1,63} =$ Table 2. Mean ERP Amplitudes and Latencies for Each Group

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Manic psychosis</th>
<th>Control</th>
<th>Significance (one-way ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amplitude (µV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>$6.5 \pm 3.8^a$</td>
<td>$5.3 \pm 3.5^b$</td>
<td>$11.6 \pm 4.1^{a,b}$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Cz</td>
<td>$9.1 \pm 4.8^a$</td>
<td>$9.1 \pm 4.2^b$</td>
<td>$16.6 \pm 5.9^{a,b}$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Pz</td>
<td>$9.7 \pm 4.9^a$</td>
<td>$10.6 \pm 4.5^b$</td>
<td>$16.0 \pm 6.4^{a,b}$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>T3</td>
<td>$4.0 \pm 1.9^a$</td>
<td>$5.4 \pm 2.4$</td>
<td>$6.8 \pm 2.2^a$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>T4</td>
<td>$4.6 \pm 2.4^a$</td>
<td>$4.7 \pm 2.6$</td>
<td>$6.3 \pm 2.0^a$</td>
<td>$p = .007$</td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>$407.4 \pm 58.6^a$</td>
<td>$385.7 \pm 50.2$</td>
<td>$369.8 \pm 25.2^{a}$</td>
<td>$p = .008$</td>
</tr>
<tr>
<td>Cz</td>
<td>$401.0 \pm 54.5$</td>
<td>$381.0 \pm 52.2$</td>
<td>$377.7 \pm 42.5$</td>
<td>ns</td>
</tr>
<tr>
<td>Pz</td>
<td>$412.6 \pm 58.0^a$</td>
<td>$396.7 \pm 45.6$</td>
<td>$381.6 \pm 34.7^{a}$</td>
<td>$p = .04$</td>
</tr>
<tr>
<td>T3</td>
<td>$411.8 \pm 65.9$</td>
<td>$403.9 \pm 47.6$</td>
<td>$383.1 \pm 30.6$</td>
<td>ns</td>
</tr>
<tr>
<td>T4</td>
<td>$402.7 \pm 49.4$</td>
<td>$407.1 \pm 44.3$</td>
<td>$378.7 \pm 28.4$</td>
<td>$p = .03^c$</td>
</tr>
</tbody>
</table>

$^a$Indicates schizophrenic and control groups significantly different on post hoc Scheffé tests ($p < .05$).

$^b$Indicates affective psychotic and control groups significantly different on post hoc Scheffé tests.

$^c$Indicates no two groups significantly different on post hoc Scheffé tests.

Figure 1. Grand averaged target waveforms for each group. Although both psychotic groups are smaller than control subjects, schizophrenic subjects show greater abnormalities over left temporal lobe (T3). As well, schizophrenics show greater abnormalities posteriorly (Pz), but bipolar subjects show greater abnormalities frontally (Fz).
0.04, \( p = .847 \); group by side interaction: \( F_{1,63} = 7.08, \ p = .01 \). Comparison of the bipolar and control groups showed that bipolar subjects were smaller than control subjects at lateral temporal sites (\( F_{1,48} = 6.13, \ p = .017 \)), but that groups showed similar lateral temporal topography (main effect of side: \( F_{1,48} = 8.01, \ p = .007 \); group by side interaction: \( F_{1,48} = 0.39, \ p = .537 \)). Finally, comparison of the schizophrenic and bipolar groups revealed that groups were not significantly different in later temporal P300 amplitude (\( F_{1,53} = 1.55, \ p = .218 \)), and that groups showed opposite lateral temporal topography (main effect of side: \( F_{1,53} = 0.14, \ p = .708 \); group by side interaction: \( F_{1,53} = 6.39, \ p = .015 \)).

Mean peak midline P300 amplitudes are presented in Figure 3. Analysis of sagittal midline amplitudes showed a significant difference in P300 amplitude between the groups (\( F_{2,82} = 20.68, \ p < .001 \)). All groups showed larger P300 posteriorly than anteriorly (main effect of site: \( F_{2,164} = 69.75, \ p < .001 \)), but this distribution differed between groups (group by site interaction: \( F_{4,164} = 2.68, \ p = .033 \)). Comparison of the schizophrenic and control groups showed that schizophrenic subjects were smaller than control subjects along the sagittal midline (\( F_{1,63} = 31.77, \ p < .001 \)). Both groups showed larger P300 posteriorly than anteriorly (main effect of site: \( F_{2,126} = 43.28, \ p < .001 \)), but this distribution differed between groups (group by site interaction: \( F_{2,126} = 2.68, \ p = .033 \)). Comparison of the bipolar and control groups showed that bipolar subjects were smaller than control subjects along the sagittal midline (\( F_{1,48} = 24.14, \ p < .001 \)). Both groups showed larger P300 posteriorly than anteriorly (main effect of site: \( F_{2,96} = 47.57, \ p < .001 \)), and this distribution did not differ between groups (group by site interaction: \( F_{2,96} = 1.83, \ p = .166 \)). Finally, comparison of the schizophrenic and bipolar groups revealed that groups were not significantly different in P300 amplitude along the sagittal midline (\( F_{1,53} = 0.00, \ p = .948 \)). Both groups showed larger P300 posteriorly than anteriorly (main effect of site: \( F_{2,106} = 53.93, \ p < .001 \)), but this distribution differed between groups (group by site interaction: \( F_{2,106} = 3.10, \ p = .049 \)).

Figure 4 presents topographic maps of P300 distribution constructed using voltage information from all 28 scalp electrodes. Figure 4, top panel, presents P300 topography from each group grand average, integrated over a peak ±25 msec interval. Maps are normalized for each group, so that zero voltage is blue and maximum voltage is magenta. The topography of P300 in schizophrenia is abnormally asymmetrical in comparison to both other groups, showing a deficit in P300 voltage on the left side. Figure 4, middle panel, shows the absolute differences in integrated peak P300 amplitude, constructed by subtracting the groups of interest. Values are normalized so that maximum group P300 amplitude differences are colored magenta. Note that the schizophrenic group showed the largest absolute amplitude differences from both control and affective psychosis groups at posterior midline and left temporal areas. The control and bipolar psychosis groups showed maximum differences over frontocentral midline areas. Figure 4, bottom panel, presents the t-test results for significant differences between groups in absolute P300 amplitude at each point on the scalp. These t-SPM maps are less conservative than the traditional, but spatially restricted, statistical approaches conducted above, and are presented to indicate more widespread patterns of topographic differences. The t-SPM maps demonstrate that the areas of maximal P300 voltage

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**Figure 2.** Mean peak lateral P300 asymmetries for each group. Note the reversed lateral asymmetry in schizophrenic subjects relative to both bipolar and control subjects.

**Figure 3.** Mean peak sagittal midline P300 distribution for each group. Note that patients show a reversed pattern of maximal reduction; schizophrenic subjects show greatest abnormality at the posterior site (Pz), but bipolar subjects show greatest abnormality at the frontal site (Fz).

**Figure 4.** Topographical maps of P300 distribution.
difference (middle panel) are not necessarily the areas of maximal statistical difference. This reflects less variance at lateral recording sites in P300 amplitude from trial to trial, since P300 amplitude increases nonlinearly toward the midline (McCarthy and Woods 1985). The schizophrenic group showed greatest statistically significant separation from the other groups at left temporal sites. The bipolar psychosis group showed greatest statistically significant separation from control subjects over the frontal area. The schizophrenic and bipolar groups showed statistically significant separation over left temporal scalp sites.

**Discussion**

Specific left temporal scalp area reductions of P300 were present in this sample of 35 chronically ill schizophrenic subjects; however, lateralized topographic abnormalities were not present in the sample of chronically ill bipolar disorder with psychotic features patients. These results suggest that lateral P300 abnormalities are specific to schizophrenia, and, moreover, are not related to psychosis in general. These P300 abnormalities may also implicate left temporal lobe structural pathology in the pathogenesis of schizophrenic signs and symptoms.

The results of this study may be confounded by overall IQ differences between the groups. Regrettably, Full-Scale IQ measures for these patients were not available; however, no subject had a borderline IQ. The literature examining relationships between P300 amplitude and IQ is inconsistent (e.g., Shimono et al 1997; Katsanis et al 1997), suggesting at best a small correlation. The results reported above remained significant when the WAIS-R subscores were used as covariates. We suggest that behavior on task is the best probe of group performance differences, and note that all group P300 differences reported remained significant when using task performance as a covariate. As well, the patient samples were on different medication regimens. Our recent analysis of

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**Figure 4.** Color-coded topographic maps of P300 voltage for a 50-msec integration interval centered about the grand average Cz peak for each group. The top maps represent the normalized voltage topography of P300 across the scalp for each group. Note that P300 is smaller on the left in the schizophrenia group (Sz), indicated by asymmetry in voltage at the middle, lateral portions of their map. The middle traces simply present the absolute differences in P300 voltage between groups. The greatest differences in both the patient groups from the control subjects (Con) are along the midline, with a somewhat greater frontal reduction in the bipolar group (BP). The greatest absolute differences in the schizophrenia and manic group are over the left temporal and parietal lobes. The bottom maps reflect the t statistic associated with the absolute group differences presented in the middle maps. Note that when the variance of P300 at the difference scalp sites is taken into account, the areas of greatest statistical separation between the schizophrenia and control groups and the schizophrenia and bipolar groups are over the left temporal lobe, and those between the bipolar and control groups are over the frontal midline.
medication effects in different samples of schizophrenia and psychotic mania found no differences in P300 amplitude or latency in subsamples on versus off lithium, on versus off klonopin, on versus off anticholinergics, and conventional versus novel neuroleptics (unpublished data, Salisbury, O’Donnell, and McCarley). Furthermore, the overall chlorpromazine equivalent score did not correlate with P300 measures, and we ourselves have shown laterality effects to be present on or off conventional neuroleptics (Faux et al 1993). Thus, this extensive analysis of medication effects in other samples suggests that medication effects in the present sample are likely to be minimal, if present at all, although they cannot categorically be ruled out.

The unilateral P300 abnormality in schizophrenia suggests an underlying structural abnormality in left temporal lobe, since our previous work in a different sample of chronically ill schizophrenic patients revealed an association between the lateralized P300 temporal reduction and the size of left posterior superior temporal gyrus (McCarley et al 1993). Furthermore, a functional or cognitive cause for the reduction might be expected to show widespread bilateral reductions, since we are unaware of any empirical evidence that inattention or resource allocation problems would cause a lateralized P300 reduction. The inference of underlying left temporal lobe pathology is also strengthened by the differences in midline distribution between schizophrenic and bipolar, and schizophrenic and control subjects. Although the exact configuration of underlying active neural tissue giving rise to the complete P300 field at the scalp cannot be derived simply from knowledge of the scalp field topography, differences in scalp topography without differences in overall amplitude unequivocally imply different patterns of underlying neural tissue activation, or different source configurations (Johnson 1993). Coupled with feasible hypotheses of generator location derived from intracerebral and scalp recordings, topographic information can provide reasonable estimates of source location. The relatively greater posterior than frontal reductions in schizophrenia point to a specific abnormality of posterior P300 generators. P300 arises in many different cortical areas (e.g., Halgren et al 1997), but only a small number of these sources are configured so that the fields can be recorded at the scalp. Posterior P300 amplitude likely reflects the summed activity of an inferior parietal source and a superior temporal gyrus source. P3 activity recorded from one electrode is not independent from the activity recorded from other nearby sites. Since electrical fields arise simultaneously across the scalp, the two bilateral posterior fields augment one another as reflected in the total amplitude at Pz. As argued previously (Salisbury et al 1998), posterior midline reductions of P300 could be at least partially explained by abnormality in one of two bilateral generators, since midline voltage reflects the summed activity of both generators. In contrast, the widespread reduction and lack of topographic difference of P300 in the psychotic bipolar relative to control subjects can be explained by either nonlateralized pathology (structural) or cognitive dysfunction (functional).

The maximal statistical differences in these two patient samples from control subjects are localized to the temporal scalp region in the schizophrenic, and the frontal scalp region in psychotic bipolar subjects (see Figure 4). These latter results are quite intriguing, given the interest in frontal lobe dysfunction in bipolar disorder. Although the literature is not entirely consistent, bipolar patients may have pathophysiological frontal lobe function and structure, including, for example, abnormalities on neuropsychological tests purportedly sensitive to frontal lobe function (e.g., WCST, Trails B; Coffman et al 1990; Morice 1990), increased white matter magnetic resonance imaging-demonstrated hyperintensities (e.g., Aylward et al 1994; Figiel et al 1991), and reduced glucose (e.g., Baxter et al 1989; Rubin et al 1995) and phosphorous metabolism (e.g., Deicken et al 1995; Kato et al 1995). Of note, inspection of the P300 voltages reported by Souza et al (1995; see their Table 3) suggests that their sample of bipolar patients also displayed an abnormally small frontal P300, although they did not explicitly examine this feature.

A topographical P300 difference between schizophrenic and psychotic bipolar subjects indicates distinct loci of cortical abnormality in these groups, since different patterns of activation in neural tissue must be proposed to account for the different scalp distribution (Johnson 1993). In the patients studied here, there is evidence of specific left posterior temporal abnormality in schizophrenia, and evidence of more anterior frontal abnormality in bipolar disorder. Of note, there was no evidence of lateralized frontal abnormality in bipolar disorder. In summary, examination of P300 topography in chronically ill schizophrenic and psychotic bipolar patients revealed that schizophrenia was associated with a specific left-lateralized posterior abnormality, suggesting underlying posterior temporal lobe pathology. In contrast this left temporal abnormality was not present in bipolar disorder, where reductions of anterior P300 voltage were present, suggesting an underlying frontal lobe pathology.

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