CLINICAL CORRELATIONS OF AUDITORY P200 TOPOGRAPHY
AND LEFT TEMPORO-CENTRAL DEFICITS IN SCHIZOPHRENIA:
A PRELIMINARY STUDY

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Summary—A number of studies using nontopographic analyses have reported an amplitude 
decrement of the auditory P200 component in schizophrenics compared to normal controls. Here 
we report a topographic analysis of the auditory P200 (204–272 ms; peak to baseline) in chronic 
medicated schizophrenics (N=11) and normal controls (N=18) and the correlation between this 
measure and clinical symptoms in schizophrenia. Exploratory T-statistic mapping (SPM) and 
"protected" Hotelling's T-squared contrasts of integrated voltages over the entire scalp showed 
that schizophrenics' P200 component had diminished amplitude in the left temporo-central region. 
Furthermore, P200 amplitude in the same scalp region during the experimental condition of counting 
infrequent tones was highly correlated with negative symptoms in the schizophrenic group.

INTRODUCTION

The auditory P200 component is a positive event-related potential which peaks about 
200 ms after the presentation of a discrete auditory stimulus, such as a tone pip. In normal 
subjects the P200 component topography is characterized by a concentric distribution with 
the largest voltage at the vertex (e.g. PICTON et al., 1974, 1978; SIMSON et al., 1977; VAUGHAN 
and RITTER, 1970; VAUGHAN et al., 1980; WOOD and WOLPAW, 1982). Although this 
potential is automatically produced regardless of task or attention variables, specific 
experimental paradigms in normals have shown that latency and amplitude of the P200 
component covaries with aspects of selective attention and stimulus encoding processes 
(PICTON and HILLYARD, 1974; OHMAN and LADER, 1977).

Since the auditory P200 component has been associated with early stimulus processing, 
the P200 may be especially relevant to the study of schizophrenia which has been similarly 
linked to deficits in stimulus processing (cf. BARBEAU-BRAUN et al., 1983). Indeed, a large 
number of studies and paradigms using nontopographic analyses have reported an amplitude 
decrement of the auditory P200 in schizophrenics compared to normal control subjects 
(ADLER et al., 1982; COHEN, 1973; COHEN et al., 1980; JONES and CALLAWAY, 1970; LIPSCHITZ 
et al., 1979; PFREIFFERBAUM et al., 1984; ROTH and CANNON, 1972; ROTH et al., 1979, 1980; 
SAITO et al., 1983; SALETU et al., 1971; SHAGASS et al., 1977, 1982). This finding appears

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to be robust over a variety of experimental paradigms and stimulus parameters, and, as
will be reviewed in the Discussion section, seems to be relatively independent of the effects
of psychoactive medication. It is unresolved, however, whether this decrement in
schizophrenia results from relatively specific underlying brain pathology or whether it is
due instead to more diffuse variables such as differences in attention, distraction, task
demands, etc. The P200 literature contains few studies comparing the effects of attention
on the same group of schizophrenics even though a wide variety of experimental conditions
have been used (e.g. Adler et al., 1982; Levit et al., 1973; Pfefferbaum et al., 1980;
Roth et al., 1980; Saletu et al., 1971; Schlor et al., 1985; Shagass et al., 1977, 1978).
We therefore considered the use of both controls for attention and a topographic analysis
of data from a complete set of electrodes to be an important first step in addressing this issue.

While scalp recordings cannot unambiguously point to underlying neural generators,
the presence of specific topographic features may be more salient to particular models of
neural pathological loci in schizophrenia than those data limited to midline recordings.
This may be particularly relevant to P200 studies where inferior parietal and auditory
temporal cortex have been implicated in P200 generation (e.g. inferior parietal regions—
Knight et al., 1987; auditory temporal cortex—Arezzo et al., 1975; Hari et al., 1980;
Peronnet and Michel, 1977; Sheer and Von Cramon, 1985; Steinschneider et al., 1980;
Vaughan and Ritter, 1970). It must be emphasized, however, that brain regions that are
not the primary sources of P200 may modulate the P200 response as a function of
experimental condition and subject set (e.g. manipulations of directed and nondirected
attention). In this regard, the cerebral blood flow studies of Roland and coworkers (1985a,b)
suggest that frontal cortex plays an especially important role in modulating the activity
present in various other cortical regions concerned with the analysis of sensory data,
including temporal–parietal regions implicated in P200 generation. Similarly, McCarley
et al. (1989) have shown, in the same subjects reported in the present study, that the degree
of frontal sulcal enlargement was strongly correlated with P200 amplitude in attentive but
not in other experimental conditions. These data are thus consistent with frontal cortex
abnormalities in schizophrenia that affect modulation of P200 activity.

Because of the possible frontal lobe–P200 modulation association and the postulated
link between negative symptoms and frontal abnormalities in schizophrenia (e.g. see reviews
by Shelton and Weinberger 1986; Weinberger 1987), we thought it particularly important
to explore systematically the possible association of P200 abnormalities in schizophrenia
with specific kinds of schizophrenic clinical symptomatology, such as positive or negative
symptoms. Such P200-clinical symptom associations could come through brain
abnormalities involved in, first of all, primary production of P200 (probably tempo-
parietal cortex) and/or, secondly, in areas concerned with modulatory effects, possibly
including frontal cortex. In the first case P200-symptom correlations might be present in
all experimental conditions and in the second case strong P200 correlations might occur
in a particular experimental condition.

In the present study, we used the technique of brain electrical activity mapping (BEAM)
to visualize the topographic distribution of the auditory P200 complex following rare and
frequent tones and experimental instructions for either directed or non-directed voluntary
attention. In all experimental conditions, schizophrenics as compared to normals had a peak-to-baseline deficiency of P200 amplitude in the left temporal–central region. However, only the amplitude of the P200 elicited by infrequent, counted stimuli had a strong correlation with negative clinical symptoms. While the small N necessitates confirmation in a subsequent study, these findings are consistent with the presence of schizophrenic abnormalities in brain areas involved in both primary production of P200 and in areas modulating P200, with deficits in modulating areas showing correlations with negative symptomatology.

METHODS

Subjects

The 11 male, medicated chronic schizophrenic subjects were those described in detail in our P300 studies (FAUX et al., 1988a,b). All subjects were recruited from a state community mental health facility, all were interviewed by one of two diagnosticians using The Schedule for Affective Disorders and Schizophrenia (SADS: SPITZER and ENDICOTT, 1978), and all were diagnosed schizophrenic using three diagnostic criteria: the DSM-III (APA Task Force, 1980), the Washington University Criteria (FEIGHNER et al., 1972), and the Research Diagnostic Criteria (RDC: SPITZER et al., 1972). Further criteria for subject selection were: between the ages of 20–45 yr; male; no history of ECT, of neurological illness or of alcohol or drug abuse. No patients were selected if they had hearing impairments, or Verbal IQs below 75. All subjects were given detailed information concerning the study protocol, and all signed informed consent.

The 11 schizophrenics were medicated with a median daily dose equivalent to 290 mg of chlorpromazime (specific neuroleptic medications included thiothixene \( N = 1 \), haloperidol \( N = 2 \), fluphenazine decanoate \( N = 2 \), fluphenazine HCL \( N = 1 \), trifluoperazine \( N = 3 \), and perphenazine \( N = 2 \), with median dosage duration approximately 6 yr). Five subjects were taking trihexyphenidyl and/or benztropine, for anti-parkinsonian effects. No other psychoactive medications (e.g. benzodiazepines, lithium, anti-depressants, etc.) were prescribed to the patients.

Ten patients were right-handed and one was left-handed; group results did not significantly differ with the presence or absence of the left-handed patient and thus his data were included. Mean values (with ranges in parentheses) for demographic information for the schizophrenic sample were: age, 33 yr (23–43); verbal WAIS-R scale, 94 (79–114); years of schooling, 13 yr (9–16.5); age of onset, 24 yr (16–32); social economic status rating (based on Hollingshead Two-factor Index of Social Position), 4.1 (where 4 = semiskilled, and 5 = unskilled; HOLLINGSHEAD, 1965); and length of time ever spent in a psychiatric hospital, 22.1 months.

The control group was the same as used in the P300 studies reported previously (FAUX et al., 1988a,b); 18 right-handed college students, with no personal or family history of psychiatric illness and no history of drug or alcohol abuse. This group had a mean age of 27 yr (ranging from 21–38), and a mean score on the verbal scale WAIS-R of 108 (ranging from 88–118). The normal and schizophrenic groups did not statistically differ in age or IQ.
MEASURES AND PROCEDURES

Electrophysiological measures

The electrophysiological measures were identical to those described in previous studies (Morstyn et al. 1983; Faux et al. 1988a,b). Briefly, auditory event-related potentials (ERPs) were averaged separately for infrequent high pitched (1070 Hz, 92 dB SPL, 15% of tones) and frequent low pitched tone pips (960 Hz, 102 dB SPL, 85% of tones) of 50 ms duration (10 ms rise time) and presented pseudorandomly at approximately 2 sec intervals in two distinct information processing conditions: (1) an inattentive, or "distractor", condition (subjects read a story) and, (2) an "attentive" condition (subjects counted the high pitched, infrequent tones). All subjects were able to perform this task with 80% accuracy or better. Separate evoked potentials were recorded for each of the four conditions: (1) Infrequent attentive (Ia), (2) Infrequent inattentive (Ii), (3) Frequent inattentive (Fi), and (4) Frequent attentive (Fa). Data was recorded from 20 scalp electrodes (international 10-20 system), referred to linked ears, and additional electrodes were placed on neck, jaw, external canthi, and immediately above and below the right eye to measure electro-ocular and muscle movement artifacts.

Prior to evoked potential averaging, the EEG was filtered using a bandpass of 0.5-50 Hz. A single evoked potential average was constructed for each electrode based upon 256 sampled data points spaced over a 1024 ms interval. Sampling began 512 ms prior to the stimulus presentation, establishing a "prestimulus baseline." EEG segments with voltages exceeding 50 μV were excluded from the average. Based upon this stringent artifact rejection criterion, individual and grand-averaged EOG and EMG waveforms were examined and showed no evidence of time-locked artifacts. Data from the set of 20 electrodes were then processed into topographic maps of electrical field distribution using the BEAM technology (Duffy et al., 1981; Duffy, 1982).

Clinical measures

The Thought Disorder Index (TDI: Johnston and Holzman 1979; Solovay et al., 1986) was used to assess thought disorder. This index includes 23 categories of thought disorder rated at four different levels of severity and it represents most of the deviant verbalizations encountered in clinical practice with psychotic patients. Patients were administered the 10 card Rorschach within 5 days of the electrophysiological measures, and in most cases within 2 days. Sessions were audio recorded, transcribed verbatim, and all peculiar, deviant, and idiosyncratic verbalizations were scored for thought disorder by a team of two judges expert in scoring the TDI. The mean rating on TDI total for the sample was 91.72 (range 7.35-451.67).

The Scale for Assessment of Negative Symptoms (SANS: Andreasen, 1981) and the Scale for Assessment of Positive Symptoms (SAPS: Andreasen, 1984) were used to rate negative and positive symptoms. The ratings for the SANS and SAPS were based on both the clinical interview (SADS) and hospital charts. The SADS was administered prior to the electrophysiological measures, usually the day before, or the morning of, testing. Interrater reliability, as measured by intraclass correlation coefficients, was 0.85 for the SAPS and 0.88 for the SANS. The items within each scale also showed high correlations with their respective global and total score ratings; ranging from 0.47 to 0.81 for the SAPS.
and from 0.73 to 0.81 for the SANS. These findings are similar to reliability studies by ANDREASEN et al. (1982a,b). The mean rating for the patients on the SANS was 9.91 (range 4-22) and the mean rating on the SAPS was 9.45 (range 3-19).

All clinical measures were scored independently of the ERP data. Spearman's Rho was used to measure correlations. This non-parametric measure is preferable for small sample sizes because it is not sensitive to distributional anomalies (SIEGEL, 1956). There were no statistically significant correlations between neuroleptic dosage level and either the clinical measures (TDI, SANS, SAPS) or the P200 measures. To reduce dimensionality of the data set, only ERP data from electrode sites that maximally differentiated normals from schizophrenics were used for correlations (these electrode sites were, parenthetically, also those which, in a post hoc analysis of all the electrode sites, most correlated with the clinical data; see Results section).

RESULTS

Part I presents the findings for P200 component amplitude differences between schizophrenics and normals. Part II uses the electrode sites that best differentiated schizophrenics from normals and correlates them with the clinical measures.

(1) SCHIZOPHRENIC-NORMAL P200 COMPONENT DIFFERENCES

(1) Topographic mapping

In each group (normal controls and schizophrenics) P200 component group topography was quite similar for all four conditions, Ii, Fi, Ia, and Fa. The Fa condition most closely matched the experimental condition used in previous P200 studies in schizophrenia, and for the sake of brevity we describe and illustrate in detail only the results from this condition.

Onset positivity of the P200 component in controls (N= 18) began at 168 ms at the vertex and developed in concentric waves that expanded laterally to engulf both hemispheres at 180 ms and had further lateral expansion at 192 ms. P200 component amplitude peaked at 204 ms; Fig. 1 depicts P200 component topography over the peak to baseline time period for both groups. In controls P200 decay was asymmetrical, with greater positive activity in left scalp regions than on the right. This left-sided voltage predominance persisted from 216 ms until reaching a baseline at about 270 ms.

P200 component topography in schizophrenics (N= 11) developed in a manner similar to normals until the peak amplitude at 192 ms was reached. However, at 204 ms (Fig. 1) a topographic asymmetry was evident that was the reverse of controls, with greater positivity in right scalp regions than on the left. This right-sided voltage predominance persisted from 216 ms until reaching a baseline at about 252 ms.

Using exploratory data analyses, we investigated these group differences within the P200 component interval (defined by the range of positivity between 168-272 ms) in two ways: (1) differences in absolute voltages and (2) differences in topography. T-statistic mapping (SPM) was used to define a time window within the P200 component interval when mean integrated amplitudes showed maximal separation between groups; in all experimental conditions the maximal statistical separation of groups was at or between 204–272 ms, the interval representing the descent of peak component positivity to baseline. During this
interval, differences between schizophrenics and normals were evident (Fig. 1) in that controls showed slightly greater voltages to the left of the vertex, and schizophrenics slightly greater to the right, with approximately the same group differences appearing in all experimental conditions (Fa, Ia, Fi, and li).

The above findings led us to conclude that the 204–272 ms time interval had several characteristics consistent across experimental conditions that made it interesting for subsequent analysis: (1) the interval maximized group voltage differences within the P200 component; (2) topographic differences between groups were evident within this interval; and (3) the interval corresponded directly to identifiable waveform landmarks (allowing for easy replication), beginning at peak component latency (204 ms) and ending at the completed descent to baseline (272 ms).

(2) Waveform morphology

The “time domain” representation of the data in Fig. 2 shows that waveforms evinced the same general trends present in the topographic maps of Fig. 1. Controls showed a P200 component maxima at Cz with lateral placements showing slightly greater amplitude on the left than on the right over the 204–272 ms interval. Schizophrenics over the same interval showed slightly more voltage over right temporal regions (T4) than left (T3). Figure 2 shows further that, although P200 amplitude for schizophrenics was clearly reduced across all scalp regions, group amplitude differences over the 204–272 ms interval in the left temporal region (T3) appeared to be larger than in the corresponding region on the right (T4). There were no statistical differences in peak component latency at the temporal and centroparietal electrode sites, although the slightly earlier peak latencies of schizophrenics compared to normals at the midline sites (Cz and Pz) is consistent with findings previously noted in the literature (Catts et al., 1986; Saletu et al., 1971).

(3) Waveform evaluation of left versus right sided differences

The SPM results suggested that left temporo-central regions produced the greatest statistical separation between groups; it does not, however, provide a direct test of group by electrode site interaction, nor does it eliminate the multiplicative effect of scalp location on amplitude (cf. McCarthy and Wood, 1985). We thus extended our SPM analyses to

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**Fig. 1.** Top, topographic distribution of P200 component activity at 204 (peak component latency), 216, 228, 240, 252, and 260 ms after auditory stimulus during the frequent attentive condition (Fa). The time interval is that from P200 peak until descent to baseline. Scaling of colors was adjusted to allow topography in lower amplitude schizophrenic group to be clearly visible and is consequently greater for this group; the color scale ranges from −4.5 to +4.5 μV in controls and −3 to +3 μV in schizophrenics. Negative voltage values are represented by blues and positive by reds, yellows, and white in ascending order. Both groups showed concentric development around the vertex, but controls showed slightly greater voltages to the left of vertex and schizophrenics slightly greater to the right throughout the interval. Bottom, t-statistic maps (SPM) show scalp regions which had the maximal statistical separation between groups during the 204–272 ms interval. Largest t-values are indicated by white, followed by red, then yellow, and with smallest values indicated by blue. SPMs highlighted the following left hemisphere scalp regions as areas of greatest between-group differences (color coded in white): the left temporal area (T3) in the Ia and Fi conditions, producing t-values between 2.90 and 3.11 (27 df) for the Ia and between 3.26 and 3.49 (27 df) for the Fi condition; the left centroparietal-temporal area (T3, C3, and P3) in the Fa condition, producing t-values between 3.62 and 3.88 (27 df); and the left central area (C3 and Cz) in the li condition, producing t-values between 2.31 and 2.48 (27 df).
FIG. 1.
FIG. 2. Grand-averaged auditory evoked potential waveforms for schizophrenics (N = 11) and normal controls (N = 18) in the frequent attentive condition (Fa). Grand-averaged waveforms indicated the same general trends made evident in the topographic data of Fig. 1 in that larger group differences in amplitude were apparent in left-sided electrode sites (T3 and T5) than were apparent in right-sided electrode sites (T4 and T6) over the 204–272 ms interval. Although the largest absolute voltage differences appeared at central electrode sites (Cz and Pz), statistical group differences at T3 are as equally large as those at Cz (see Fig. 1, Fa SPM) because of the lower T3 variance. Voltage origins at time zero for each group were established by a 500 ms prestimulus baseline (not shown) which averaged zero microvolts over the interval.

The same two non-SPM statistical procedures previously described for our P300 studies: (1) a simple left/right voltage ratio measurement to test for asymmetry and, (2) a multivariate analysis.

**Left/right ratio.** This measurement consists of a simple ratio measurement of the mean integrated amplitude of P200 from 204 to 272 ms for left (e.g. T3) vs right (e.g. T4) electrodes for each subject. Table 1 expresses the group geometric mean ratios in logarithmic

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Schizophrenics</th>
<th>Normals</th>
<th>Mann-Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 / T4</td>
<td>−0.24 (−.79)</td>
<td>0.25 (1.28)</td>
<td>P &lt; 0.025</td>
</tr>
<tr>
<td>C3 / C4</td>
<td>−0.14 (−.87)</td>
<td>0.18 (1.20)</td>
<td>ns</td>
</tr>
<tr>
<td>T5 / T6</td>
<td>0.00 (1.00)</td>
<td>0.37 (1.44)</td>
<td>ns</td>
</tr>
<tr>
<td>P3 / P4</td>
<td>0.14 (1.15)</td>
<td>0.18 (1.20)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: ratios consisted of mean integrated amplitude of P200 (204–272 ms) for left versus right electrodes. The geometric mean (in parentheses) was computed by taking the exponential of the mean of the logarithms of the ratios. For these computations we uniformly added a baseline constant of +0.1 to each electrode value to prevent division by zero. Logarithmic means are positive when the left side has maximal amplitude, and negative when the right side has maximal amplitude. Near zero values indicate equality. The probability values are from a two-sided Mann-Whitney U-test.
form so as to show positive values when the left side is predominant, and negative values when the right side is predominant. On the T3/T4 ratio, schizophrenics had a left < right temporal region pattern that was statistically different from the left > right pattern of normals, a result consistent with both the SPM and waveform analyses.

Hotelling's $T$-squared analysis. The second non-SPM quantitative analysis was a multivariate statistical analysis using mean integrated amplitude values specific to electrode sites over the centroparietal and temporal areas (Fig. 3). Hotelling's $T$-squared test provides a "protected" multiple $t$-test and a direct test of topographic differences based on a test of interaction between groups and electrode sites. Figure 3 illustrates the overall discrimination of these scalp regions between schizophrenics and controls ($F$ equivalent to Hotelling's $T$-square = 4.87, $df = 5, 23, p < 0.05$). However, on test of individual electrode sites against Hotelling's $T$-criterion (equalling 3.94 for $p < 0.05$) only the left and midline scalp regions were statistically significant, a finding compatible with the SPM analysis.

With respect to lateralization, Fig. 3 shows that left scalp regions in normals had slightly higher amplitudes than corresponding regions on the right, and that this trend was reversed.
in schizophrenics. This apparent group by electrode site interaction, tested by Hotelling's $T$-Squared "profile analysis of parallelism" was statistically significant ($F$ equivalent to Hotelling's $T$-square = 5.28, df = 4, 24, $P < 0.05$). This interaction was statistically different ($F(4,24) = 4.00$, $P < 0.05$) when amplitude data between groups was normalized (using a transformation from McCarthy and Wood, 1985).

(4) Schizophrenic–normal group separation vs overlap

To test the degree of overlap between individuals in the two groups, the putative differentiating feature of mean integrated (204–272 ms) amplitude was calculated for each individual over the left controparietal–temporal scalp region in the Fa condition. Using this feature, groups showed significant statistical separation (see Fig. 4), schizophrenics yielding a mean of 0.82 $\mu$V and the controls a mean of 3.10 $\mu$V ($t = 4.69$, df = 27, $P < 0.001$). To describe the effectiveness of this feature, we used a separation line of 1.8 $\mu$V that kept overlap values the same for both groups (Fig. 4); this line correctly separated 14/18 normals and 8/11 schizophrenics.

![Fig. 4. Separation of schizophrenics and normals by P200 amplitude. This 1.8 $\mu$V criterion correctly categorized 14/18 normal controls and 8/11 schizophrenics. (P200 values are mean integrated amplitude (204–272 ms) over the scalp region producing maximal statistical separation between groups; see Fig. 2, Fa SPM).](image)

(II) CLINICAL CORRELATIONS OF THE AUDITORY P200 COMPONENT FOR SCHIZOPHRENICS

(1) Overview

This section examines the clinical correlates of P200 waveform amplitude as a function of both experimental condition (i.e. Infrequent attentive, Frequent attentive, Infrequent inattentive, and Frequent inattentive) and scalp region. Since the group topographic
waveform separation between normals and schizophrenics was maximal at T3, C3, Cz, C4, and T4 electrode sites (see Part I), we present only these results. The basic structure of the data set is a matrix of dimension $4 \times 5 \times 4$: i.e. Four Sets of Clinical Scales (SANS, SAPS, TDI and CLINICAL STATUS) $\times$ Five Electrode Sites (T3, C3, Cz, C4, and T4) $\times$ each of Four Experimental Conditions (Infrequent attentive, Frequent attentive, Frequent inattentive and Infrequent inattentive). This matrix is shown in Table 2, and the patterns of association are graphically displayed in Fig. 5. Visible in this figure is a strong association between P200 amplitude and the SANS scale in the Infrequent attentive condition; a less strong association is present between P200 amplitude and the SAPS/TDI scales in the Frequent attentive condition.

**Table 2. Number of statistically significant correlations (Spearman's rho $P < 0.05$) between P200 integrated amplitude at T3, C3, Cz, C4, and T4 electrode sites for the four experimental conditions and the SANS, SAPS, TDI, and clinical status measures (total score and all sub-scales). A plus indicates positive— and a minus negative—valued $\rho$s.**

<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>Electrode sites</th>
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<tbody>
<tr>
<td></td>
<td>T3</td>
</tr>
<tr>
<td>SANS</td>
<td></td>
</tr>
<tr>
<td>$la$</td>
<td>+4</td>
</tr>
<tr>
<td>$Fa$</td>
<td>+1</td>
</tr>
<tr>
<td>$li$</td>
<td>0</td>
</tr>
<tr>
<td>$Fi$</td>
<td>0</td>
</tr>
<tr>
<td>SAPS</td>
<td></td>
</tr>
<tr>
<td>$la$</td>
<td>0</td>
</tr>
<tr>
<td>$Fa$</td>
<td>-1</td>
</tr>
<tr>
<td>$li$</td>
<td>0</td>
</tr>
<tr>
<td>$Fi$</td>
<td>+4</td>
</tr>
<tr>
<td>TDI</td>
<td></td>
</tr>
<tr>
<td>$la$</td>
<td>+3</td>
</tr>
<tr>
<td>$Fa$</td>
<td>-6</td>
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<tr>
<td>$li$</td>
<td>-1</td>
</tr>
<tr>
<td>$Fi$</td>
<td>+5</td>
</tr>
<tr>
<td>Clinical Status</td>
<td></td>
</tr>
<tr>
<td>$la$</td>
<td>-1</td>
</tr>
<tr>
<td>$Fa$</td>
<td>0</td>
</tr>
<tr>
<td>$li$</td>
<td>0</td>
</tr>
<tr>
<td>$Fi$</td>
<td>+3</td>
</tr>
<tr>
<td>Total number of correlations</td>
<td>33</td>
</tr>
</tbody>
</table>

While the basic data set is amenable to multivariate analysis, the small sample size relative to the large number of variables vitiates the power of this kind of statistical analysis. Thus when multivariate regression analyses of 5 sites $\times$ 4 conditions $\times$ total score for the SANS, SAPS, and TDI were performed, no statistical significance was noted even though individual Spearman's rank order correlations were high (e.g. 0.64 for SANS total and 1a P200 amplitude), as detailed below. Thus, the cluster of associations between experimental condition and the clinical scales that we shall describe must be regarded as the product of an exploratory data analysis and requiring replication in a subsequent study. The sections below describe the observed associations with the SANS, SAPS, and TDI scales; for reasons
of brevity the clinical status variables, which had fewer associations, will not be presented further.

(2) Negative symptoms

Figure 5 and Table 2 show that the Infrequent attentive condition produced a high number of P200 correlations with the SANS scale, a total of 20 compared with only 4 in the Frequent attentive condition and zero in both the Infrequent and Frequent inattentive conditions (Ii, Fi). A left central predominance in the number of statistically significant correlations in the Infrequent attentive condition was also evident: T3/C3 (left) sites had 9 statistically
significant correlations, whereas C4/T4 (right) sites had only 6. Furthermore, averaging across electrode sites, the Spearman’s rho between the 1a condition P200 amplitudes and the clinical measures (SANS, SAPS, TDI) was high and statistically significant (P < 0.03; Table 3).

Table 3. Spearman rho correlations between the total score on SAPS, SANS, and TDI and the average of P200 component amplitude (204–272 ms) across T3, C3, Cz, C4, T4 electrode sites as a function of experimental condition

<table>
<thead>
<tr>
<th>Clinical scales</th>
<th>SAPS</th>
<th>SANS</th>
<th>TDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent Attentive (1a)</td>
<td>-0.26</td>
<td>0.64*</td>
<td>-0.18</td>
</tr>
<tr>
<td>Frequent Attentive (Fa)</td>
<td>0.60*</td>
<td>0.36</td>
<td>-0.56</td>
</tr>
<tr>
<td>Infrequent Inattentive (1i)</td>
<td>-0.23</td>
<td>0.17</td>
<td>-0.25</td>
</tr>
<tr>
<td>Frequent Inattentive (Fi)</td>
<td>-0.24</td>
<td>0.12</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

*P < 0.05.

Figure 6 provides additional details on the statistically significant correlations in the Infrequent attentive condition between P200 amplitude at the various electrode sites and the items comprising the SANS; the left central predominance of the significant correlations for the SANS sub-scales and the total score is noteworthy. The magnitude of the left central total SANS score correlations is also of note; all rhos were greater than 0.60. Furthermore, all sub-scales save for attentional impairment were statistically significant for both the C3 and Cz sites, with rhos ranging from 0.57 to 0.74 for the C3 site and from 0.55 to 0.67 for the Cz site. The anhedonia sub-scale had statistically significant rhos for P200 amplitude at all 5 electrode sites. All significant correlations were positive in sign.

3) Positive symptoms (TDI and SAPS)

In general the correlations between P200 amplitude and positive symptoms (SAPS and TDI) were less than those for the SANS in terms of the percentage of rhos that were statistically significant. As shown in Fig. 5, the SANS showed two P200 electrode sites with rho percentage values greater than 80% and two others greater than 60%, whereas for SAPS/TDI, combined, only one electrode site had percentages values greater than 60%. Also, in contrast to the SANS, most of the SAPS/TDI measures had negative correlations in the Attentive conditions. The SAPS correlations showed a topographically central distribution with a left bias. For the TDI correlations, the left electrode sites were most important. Averaging over all electrode sites, Spearman’s rho correlation between P200 amplitude in the Fa condition and the SAPS scale was statistically significant (P < 0.05; Table 3).

4) Orthogonality of P200 and P300 waveform correlations and comparison of correlations with positive and negative symptoms

For an analysis of the correlation between P200 and P300 waveforms in schizophrenics we used the electrode sites which most differentiated schizophrenics from normal controls in both the P200 and P300 studies. For the P300 studies (see Faux et al., 1988a,b) this
Fig. 6. Statistically significant Spearman's rho correlations between P200 electrode sites and the SANS for the Infrequent Attentive condition.
FIG. 7. Spearman *rho* correlations between the Z transformed values of SAPS, SANS total score and the Left Temporal Feature of the P300 (LTFP300g) and between the Z transformed values of the SAPS, SANS total scores and the P200 at the T3 electrode site for the Infrequent Attentive condition (T3P200Ia).

consisted of the left temporal feature (Goodin subtraction P300, or LTF-P300g) comprised of the amplitude at left temporal electrode sites (T3 and T5) integrated over the P300 interval of 296–396 ms. For the P200 waveform this was the T3 electrode site in all four experimental conditions with amplitude integrated over 204–272ms. Spearman rank order correlations between the LTF-P300g and the T3–P200 in each of the four experimental conditions showed *no* statistically significant *rhos*. Thus, the hypothesis of orthogonality of these waveforms could not be rejected. Furthermore, there was a different association between P300 and P200 and clinical symptoms in the same patient group, as shown in Fig. 7, where the P300 measure is seen to be highly correlated with SAPS but not SANS, while the P200 feature in the Infrequent Attentive condition is highly correlated with SANS but not SAPS.

**DISCUSSION**

Our P200 data are consistent with previous non-topographic analyses showing middle latency evoked potential amplitude decrements in schizophrenics relative to normals (Adler
Our topographic data have further indicated that the decrement is most prominent in left temporo-central scalp regions. The schizophrenic group’s P200 component (peak to baseline) showed a tendency toward a right-deviated positive maximum in color mapping, while normal controls showed a slight left-deviated positive maximum. Schizophrenics showed deficient P200 activity in the left temporo-central region as demonstrated by (1) t-statistic mapping (SPM), (2) the ratio of left temporal amplitude to right temporal amplitude, (3) Hotelling’s T-squared “protected” contrasts of the left temporal and left central regions, and (4) profile analysis of parallelism. In marked contrast to the P200 amplitude differences which were present in all experimental conditions, the clinical correlations were quite condition-specific. The most prominent of them was with negative symptoms, as measured by the SANS scale, and occurred with the P200 waveform following the infrequent (counted) stimulus in the attentive condition. These correlations were most prominent at left temporal and left central electrode sites, where Spearman’s rhos were in the 0.5–0.7 range. The implications and interpretations of these findings are given below.

**P200 topography and generator loci**

With respect to possible localizing inferences, this sample of schizophrenics showed P200 topographic deficits in areas consistent with putative temporo-parietal generator loci for the P200. These include the primary and secondary auditory cortices, based on dipole modeling studies (citations in Introduction) and the fact that symmetrical deficits in middle latency auditory components, similar to those we have seen in schizophrenics, have been reported in patients with unilateral damage to temporal cortex (Peronnet and Michel, 1977; Wood et al., 1984). The more recent Knight et al. (1987) work points to inferior parietal gyrus, since stroke lesions of this gyrus abolished P200 ms latency components while superior temporal gyrus lesions did not. It is important to underline the caution that our scalp recordings, while consistent with such localization, cannot themselves unambiguously localize neural generators, and further converging studies are essential, especially those using techniques, such as MRI and PET, that offer more certain structural localization.

Furthermore, it is also likely that, even if temporo-parietal cortex is important as a primary generator locus, many other brain areas provide important modulatory input. We tentatively suggest that the presence, in all conditions, of P200 waveform deficits in schizophrenics in our data, may reflect a deficit in primary temporo-parietal generator areas, whereas the condition-specific correlation of clinical data with P200 may result from abnormalities of modulatory input, with one important modulatory area being frontal cortex. While speculative, such a model would be consistent with preliminary CT data from the same schizophrenic group reported here indicating that, within the schizophrenic group, P200 amplitude, in the infrequent attentive condition but not the other conditions, was strongly correlated with the degree of frontal lobe pathology, as indicated by sulcal and interhemispheric fissure enlargement, in the infrequent attentive condition but not the other conditions (McCarley et al., 1989). We emphasize such interpretations about relationships between ERPs and brain regional pathology are hypotheses that must be further tested.
P200 topography and waveform differences between schizophrenics and normals

The compatibility of our topographic findings with those in the existing literature is somewhat unclear because no previous studies have examined the same P200 component time window (204–272 ms, peak to baseline) used in our analysis, and our findings of maximal statistical differences between groups in left scalp regions may not hold true for other time segments. In our data, group differences in amplitude and topography were evident only during the descending phase of the P200 component. Non-topographic studies have reported schizophrenic vs normal differences in ascending (N100–P200) and/or descending (P200–N200) phases of the P200 component (Adler et al., 1982; Cohen, 1973; Cohen et al., 1980; Jones and Callaway, 1970; Lifshitz et al., 1979; Roth and Cannon, 1972; Pfeifferbaum et al., 1984; Roth et al., 1979, 1980; Saitoh et al., 1983; Salletu et al., 1971; Shagass et al., 1977, 1982). In general, however, our choice of the 204–272 ms time window appears appropriate for our data because this interval: (1) maximized the statistical differences between groups; (2) showed consistently left-sided amplitude deficits in schizophrenics across experimental conditions; (3) revealed topographic differences between groups; and (4) was easily interpretable in terms of waveform morphology (peak to baseline). Nonetheless we emphasize the need for a subsequent confirmatory study before these differences can be regarded as solidly established.

P200-clinical correlations

The most striking P200-clinical correlation in the present study was the association between P200 amplitude and negative symptoms in the Infrequent attentive condition. The paucity of correlations between P200 measures and clinical symptomatology found in previous studies (e.g. Roth et al., 1980) likely stem from three major differences in methodology: (1) almost all previous studies have used only a single experimental condition for the P200, most closely akin to our Frequent attentive condition, and would therefore have missed any correlations specific to other experimental conditions; (2) Previous studies have tended to use measures of peak amplitude at central electrodes, measures which may not maximally discriminate schizophrenics from controls, and which therefore may not maximize the associations of symptomatology and electrophysiology; and (3) the more recently developed psychopathology measures used by us (e.g. TDI, SAPS, SANS) probably have better reliability than those available for earlier studies.

We think it important that the four experimental conditions (e.g. frequent and infrequent tones, and attentive and inattentive conditions) did not provide equivalent information with respect to correlations with the clinical data for the P200, a situation we had shown previously to be true for the P300-clinical correlations (Shenton et al., 1989). As previously stated, from a theoretical point of view this is not surprising under our model postulating that P200 amplitude is likely under control of multiple generators, both primary and modulatory, whose level of activity changes with experimental condition.

Another interesting aspect of the schizophrenic group SANS-P200 correlations was that they were positive, indicating that relatively high values of P200 were correlated with high levels of negative symptoms, although the schizophrenic group as a whole differed from the normal group by showing a P200 amplitude deficit. As noted earlier, we think it possible
that the Infrequent attentive condition-specific SANS-P200 component correlation may result from abnormalities of a brain region modulating the primary temporo-parietal neocortical P200 neural generators, and this abnormality may modulate the overall schizophrenic group P200 deficit and produce the characteristic within group clinical correlations. Our CT data showing a strong (and also positive) correlation between CT evidence of frontal sulcal enlargement and P200 amplitude in this same patient group (MCCARLEY et al., 1988) are compatible with this explanation and a modulatory source in frontal lobe, a brain region previously implicated in modulation of sensory input (ROLAND, 1985). It is also possible that, in the schizophrenic group, factor(s) associated with attempted compensation for deficits may account for the within group correlations.

Comparisons between P200 and P300 in schizophrenia

That P200 correlated maximally with negative symptoms in schizophrenia is in marked contrast to our P300 studies (FAUX et al., 1988 a,b). Using the P300 derived from the same stimulus presentations in the same group of patients, we found the highest level of P300 correlation to be with positive symptoms, as measured by the SAPS and TDI (see SHENTON et al., 1988). In addition, the low P200-P300 waveform correlations suggest that these two ERP components may be tapping different aspects of brain function and, consequently, may prove to be useful probe pairs in studies exploring brain processing related to positive and negative symptoms in schizophrenia. The absence of P200-P300 waveform correlations and the existence of a recent study (KNIGHT et al., 1987) showing differential P200 and P300 effects (oddball paradigm) of temporal and parietal lobe lesions should be underlined. These findings reinforce the possibility of different aspects of brain processing of the oddball stimuli being reflected at different time points of the ERP, and hence of the possibility of P200 and P300 components being associated with different clinical symptoms.

Limits on generalizations from findings

Three caveats to generalizations from this study should be reviewed.
(1) The relatively small N of this study yielded definite patterns of correlation between clinical scales and the P200 amplitude in different experimental conditions. The data set is, however, exploratory and should be regarded as tentative until the findings can be replicated in a larger patient group.
(2) Our patients were medicated and it is not known with certainty what effect this might have on the correlations between our topographic electrophysiological measures and the clinical data set. However, it is important to emphasize that, in non-topographic studies, P200 amplitude reductions in schizophrenia have been replicated numerous times in unmedicated schizophrenics (ADLER et al., 1982; LIFSHTZ et al., 1979; SHAGASS et al., 1977, 1978, 1982), as well as in medicated schizophrenics (COHEN et al., 1980; JONES and CALLAWAY, 1979; ROTH and CANNON, 1972; ROTH et al., 1980; SATOH et al., 1983; SALETU et al., 1971). Further, studies directly comparing medicated and unmedicated patients have found no medication group effects on P200 amplitude (LIFSHTZ et al., 1979; PFEFFERBAUM et al., 1980; ROTH et al., 1980, 1981). However, acutely disturbed patients tested pre- and post-medication have shown P200-N200 amplitude increases after medication (SAKALIS et al., 1972; SCHLOR et al., 1985). Thus the P200 literature does not indicate that medication
by itself induces a midline electrode amplitude reduction in schizophrenics. The present study found no correlation between neuroleptic level and P200 amplitude. Nonetheless, it is important for us to include unmedicated patients in future studies in order to rule out medication effects as a possible confound.

(3) We have not addressed the specificity of our findings to schizophrenia, as compared with, for example, other major psychoses. In previous non-topographic studies PFEFFERBAUM et al. (1984) have found P200 amplitude reductions in demented patients, primarily Alzheimer's type, and in tricyclic-medicated but not in unmedicated depressives. SHAGASS et al. (1977, 1978) compared a variety of psychiatric disorders, such as neurotics, psychotic depressives, chronic and acute schizophrenics, and manic-depressives, on the auditory P200 and found that only the chronic schizophrenics and the psychotically depressed showed amplitude reductions relative to normal controls. Thus while our focus on well-defined, unambiguous cases of schizophrenia was a necessary first step, future studies will include a control group with other psychiatric diagnoses.

In summary, our data provide preliminary evidence for a left temporo-central deficiency and a right-deviated positive maximum in the P200 topography of schizophrenics relative to that of normal controls. Furthermore, within the schizophrenics group, high correlations between P200 amplitude and negative symptoms were condition-specific (Infrequent attentive condition, the counting condition). These data are compatible with other structural, metabolic, histological, and electrophysiological studies suggesting both temporal and frontal lobe pathology in schizophrenia (McCARLEY et al., 1989; SHELDON and WEINBERGER, 1986; WEINBERGER, 1987; ZEC and WEINBERGER, 1986).

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P200 CLINICAL CORRELATES


