Correlations Between Abnormal Auditory P300 Topography and Positive Symptoms in Schizophrenia: A Preliminary Report

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P300 component amplitude in the left temporal scalp region, shown in three previous studies to differentiate normals from schizophrenics, was found to be significantly correlated with the Thought Disorder Index (TDI) and the Scale for the Assessment of Positive Symptoms (SAPS). These correlations occurred primarily in the P300 waveform derived from the Goodin paradigm. These findings suggest a brain processing disturbance in positive symptom schizophrenia that may be reflected by electrophysiological abnormalities detectable in the temporal scalp region.

Introduction

In three separate topographic studies, our laboratory has reported a left temporal scalp region amplitude decrement of the auditory P300 in schizophrenics compared with age-matched normal controls (Goodin subtraction procedure, P300g waveform) (Morstyn et al. 1983; Faux et al. 1988a–c). As this left temporal feature was shown to differentiate schizophrenics from normal control subjects, and as there is little information regarding the relationship of evoked potentials to clinical variables in schizophrenia (e.g., Saletu et al. 1971; Roth and Cannon 1972; Roth et al. 1980a, b), we extended our analyses by examining the relationship between this feature and specific types of clinical symptoms in schizophrenia. We correlated the auditory event-related potential data from the same schizophrenic patients used in the replication study (see Faux et al. 1988a) with data collected concurrently from the Thought Disorder Index (TDI) (Johnston and Holzman 1979), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1981), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1981).
Clinical Correlates of P300 Deficit in Schizophrenia

(Andreasen 1984), and from clinical status measures (e.g., age of onset and medication dosage level).

Methods

Subjects

The 11 male, medicated (median daily dose equivalent to 290 mg of chlorpromazine) chronic schizophrenic subjects were those described in detail in our P300 replication study (Faux et al. 1988a). Ten patients were right-handed. All met the criteria for schizophrenia based on the DSM-III (APA 1980), the Washington University Criteria (Feighner et al. 1972), and the Research Diagnostic Criteria (Spitzer et al. 1978), and all gave informed consent.

Measures and Procedures

Clinical Measures. The Thought Disorder Index (Johnston and Holzman 1979; Solovay et al. 1986) was used to assess thought disorder. Patients were administered the 10 card Rorschach; responses were audio recorded, transcribed verbatim, and then scored by two expert judges. Information from SADS interviews (Spitzer and Endicott 1978) and chart reviews was used to rate patients on negative and positive symptoms using Andreasen's SANS and SAPS (Andreasen 1981, 1984) scales. Interrater reliability was 0.849 for the SANS and 0.881 for the SANS.

Electrophysiological Measures. The electrophysiological measures have been described in detail elsewhere (Morstyn et al. 1983; Faux et al. 1988a). Briefly, auditory event-related potentials (ERPs) were averaged separately for infrequent high-pitched (15%) and frequent low-pitched tone pips in an inattentive, or "distractor," condition (subjects read a book) and in an attentive condition (subjects counted rare tones). ERP data were recorded from 20 scalp electrodes (international 10–20 system) referred to linked ears. Electro-oculogram (EOG) and electromyogram (EMG) were also monitored for artifact rejection. ERPs were produced in four conditions: infrequent inattentive (Ii), frequent inattentive (Fi), infrequent attentive (Ia), and frequent attentive (Fa). The P300g waveform was then calculated according to the Goodin subtraction procedure—P300g = (Ia – Fa) – (Ii – Fi) (Faux et al. 1988b)—and was then processed into topographic voltage maps (Duffy et al. 1981, 1982). P300g amplitude values were integrated over the P300g time interval, 296–396 msec, as this interval most differentiated schizophrenics from normals.

To reduce dimensionality of the data set, only ERP data from electrode sites that maximally differentiated the normal and schizophrenic groups were used for correlations. These electrode sites were: (1) the average of the T3 and T5 electrode P300g amplitudes, termed the "left temporal feature" (LTF) (Faux et al. 1988a); (2) T3 electrode for the infrequent attentive condition waveform (Ia) and the attentive condition subtraction waveform (Ia – Fa); and (3) F7 electrode for the inattentive condition subtraction waveform (distract-condition, Ii – Fi).

All clinical measures were scored independently of the ERP data. Spearman’s rho was used to measure correlations. This nonparametric measure is preferable for small samples, as 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, or SAPS scores) or the P300 measures.
Results

Only the correlation coefficients between clinical and ERP data will be reported here (for actual ERP waveforms see Faux et al. 1988a,b). Figure 1 shows that the major set of statistically significant correlations was between the P300g, left temporal feature (LTF, T3 and T5 electrode sites) and the SAPS and TDI. There were no significant correlations with either the SANS or with the group of clinical status variables. For the P300g, there were 16 statistically significant correlations observed out of 46 total correlations (see Figure 1; Fisher’s exact ratio predicts 2.6 by chance; binomial test indicates expected proportion of 0.05, observed proportion 0.347, \( p \leq 0.0001 \)). Figure 2 summarizes the relationship between each individual patient’s score on the P300g LTF and the total SAPS (both scores normalized to z-values).

In contrast to the P300g correlations, the Ia waveform (T3 electrode site) and clinical-variable correlations were, in general, nonsignificant, and the number of statistically significant correlations, given the number of correlations performed, was not greater than expected by chance (see Figure 1; Fisher’s exact ratio = 2.6 expected by chance, 2 were observed; binomial test, \( p < 1.00 \)).

As the Ia – Fa attentive condition subtraction waveform and its individual components did not account for the high number of correlations seen between the psychopathology measures and the P300g, this suggested that the major contribution came from the inattentive condition waveforms: Ii, Fi, and Ii – Fi.

Figure 1 shows the clinical correlations with the electrophysiological measures at the left frontotemporal site (F7), where the inattentive condition waveform (Ii – Fi) differences between the schizophrenic and normal groups were at a maximum. This waveform, like the P300g waveform, showed statistically significant correlations with the TDI and SAPS clinical variables, although reversed in sign. The Ii – Fi waveform was also statistically significantly correlated with the total SANS score and with the Alogia subscale of the SANS. For this waveform, Fisher’s exact ratio predicts 2.6 correlations expected by chance, but 10 statistically significant correlations were observed; the binomial test, with an expected proportion of 0.05, showed the observed proportion of 0.217 to have a \( p \leq 0.0001 \). The individual Ii and Fi waveforms were not so robustly correlated (not shown in Figure 1).

Figure 1. Correlations between psychopathology measures and the left temporal feature (LTF) of the Goodin paradigm waveform (P300g) and its component waveforms: Ia, infrequent attentive; Ia – Fa, attentive condition subtraction; and Ii – Fi, inattentive condition subtraction. Spearman’s rho was used to correlate the clinical data with the P300 data and the \( p \) values are \( \leq 0.05 \) unless otherwise specified. Additionally, because the ratio of the number of variables to the number of subjects was high, we incorporated both Fisher’s exact ratio and binomial tests of probability to control for the effects of multiple correlations on significance probability levels. There were a total of 46 correlations performed for each of the waveforms: 6 for the SANS, 7 for the SAPS, 9 for the clinical status variables, and 24 for the TDI (only 14 of the 24 are listed below). Note: Total Hospitalization, number of months from first psychiatric hospitalization to present; Net Hospitalization, number of months ever spent in psychiatric hospital; Present Hospitalization, number of months of current episode; Percent Hospitalization, number of months ever spent in psychiatric hospital divided by the number of months at risk (Total Hospitalization). Note: Only TDI categories that showed statistical significance are presented (14 of 24).
Clinical Correlates of P300 Deficit in Schizophrenia
Figure 2. (Top) Correlations between the Z-scores for the Scale for the Assessment of Positive Symptoms (SAPS) and the left temporal feature (LTF) for each of the 11 schizophrenic patients (a through k) and (Bottom) between the Scale for the Assessment of Negative Symptoms (SANS) and the left temporal feature (LTF) for the same patients. \( N = 11 \) schizophrenics.

Discussion

The goal of the present study was to explore the relationship between neurophysiological and clinical indices of dysfunction in schizophrenia. We reported a number of high correlations between auditory P300 component amplitude (over 296–396-msec interval) in the left temporal scalp region and positive symptoms (TDI and SAPS) in schizophrenia. Compared with previous studies, the number and strength of correlations was high, a result we attribute to (1) the use of the Goodin paradigm—the P300 Ia waveform used by most studies here showed only weak correlations (e.g., Saletu et al. 1971; Roth and Cannon 1972); and (2) the inclusion of more reliable and specific assessments of psychopathology, i.e., the TDI, SAPS, and SANS.

These correlations, although strong and unequivocal, nonetheless have an apparently paradoxical aspect: within the schizophrenic group, a high amplitude P300e LTF was associated with symptomatology, but between normal and schizophrenic groups, the presence of a high amplitude LTF was found to be characteristic of normals and a low
amplitude LTF of schizophrenics (Morstyn et al. 1983; Faux et al. 1988a–c). This finding may partly result from the fact that the P300\textsubscript{LTF} is formed by a subtraction of the inattentive condition waveform (Ii − Fi), which shows a negative correlation between waveform amplitude and positive symptoms. Another possible explanation is that the positive-signed P300\textsubscript{LTF}-positive symptom correlation may reflect the presence of two factors, one responsible for the overall schizophrenic–normal difference and another operating within the schizophrenic group and reflecting secondary or compensatory processes.

Further interpretations must await future studies. Additional work is needed to determine the generalizability of our findings and to address some of their limitations, such as (1) small sample size, (2) possible effects of medication (see, however, Blackwood et al. 1987), (3) lack of a psychopathological contrast group, and (4) need for more explicit experimental control over attentional factors (Nestor et al. 1988).

Though one should limit any generalizations from our present study, one very plausible interpretation of our data is that schizophrenic patients process information in a qualitatively different way from normal control subjects, and this difference, with the concomitant occurrence of thought disorders and positive symptoms, may be related to electrophysiological alterations detectable in the left temporal scalp region. Although scalp recordings do not uniquely define generator loci, in a CT study utilizing the same patients, we found that both the P300\textsubscript{LTF} left temporal abnormality and the SAPS measure of positive symptoms are highly and significantly correlated with the extent of left Sylvian fissure enlargement (McCarley et al. 1989). Thus, both the positive symptom correlation and P300\textsubscript{LTF} electrophysiology may reflect temporal lobe alterations in schizophrenia, a locus increasingly implicated in schizophrenic pathology (e.g., Reynolds 1983; Bogerts et al. 1985; Brown et al. 1986; Crow 1986). Further, although the use of linked ears reference may make lateralized ERP effects difficult to evaluate (Nunez 1981), our laboratory’s recent data, using a nose reference, have shown the same left temporal P300 deficit in schizophrenia (Faux et al. 1988c), confirming its presence.

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