Cognitive Brain Potentials in Children at Risk for Schizophrenia: Preliminary Findings

by David Friedman, Herbert G. Vaughan, Jr., and L. Erlenmeyer-Kimling

Abstract

Event-related brain potentials were recorded to auditory stimuli from children at risk for schizophrenia and normal control children who were part of two independent samples being followed longitudinally. Subjects were required to detect (with a reaction time response) one of two infrequent events (either a pitch change or a missing stimulus), each of which occurred 17 percent of the time, and was embedded in a sequence of frequent events occurring 66 percent of the time. The event-related potential (ERP) elicited by both infrequent stimuli consisted of a positive-going wave peaking at 350 msec for the pitch change ERP (P350) and 400 msec for the missing stimulus ERP (P400) and a slow wave, which overlapped with and extended beyond the P350 and P400 potentials. When the eliciting event was relevant, these potentials were significantly larger than when it was irrelevant. When the waveform produced by the high-risk (HR) subjects were compared to those produced by the normal control (NC) subjects, the HR subjects of both samples showed significantly less late positive amplitude (P350 and P400) than the NC subjects, but only when the eliciting event was relevant. This effect appeared to be independent of reaction time, as reaction time means and variances were quite similar between risk groups. Other possible explanations for this amplitude reduction were explored. Since late positive component amplitude reduction has been consistently reported to characterize the waveforms of adult schizophrenics, the reduction seen in children at genetic risk for schizophrenia may be a premorbid indicator for the development of the psychosis.

The psychophysiological functioning of adult schizophrenics has been well documented in the past two decades (see, for example, reviews by Shagass 1976; Buchsbaum 1977; Roth 1977; Shagass 1977; Venables 1977; Zahn 1977; Spohn and Patterson 1979) but it is only recently, with the advent of the high-risk longitudinal study (e.g., Mednick and McNeil 1968), that the psychophysiological functioning of their offspring has come under investigation. In this method of study, the children of schizophrenic parents are chosen as subjects because they are at greater than usual statistical risk for the development of schizophrenia (Erlenmeyer-Kimling 1968; Zerbin-Rudin 1967).

The tasks and stimulus parameters used with these children have come from those used with adult schizophrenics since, if it is assumed that the disorder is, at least in part, genetically determined, a dysfunction found in the adult might also be demonstrable in the child at genetic risk.

One of the most consistent event-related potential (ERP) findings with adult schizophrenics has been the reduction, relative to controls, in late positive component (P300) amplitude (Roth and Cannon 1972; Levit, Sutton, and Zubin 1973; Verleger and Cohen 1978).

Reprint requests should be sent to Dr. D. Friedman, Department of Medical Genetics, New York State Psychiatric Institute, 722 W. 168th Street, New York, NY 10032.
Timsit-Berthier and Gerono 1979; Pass et al. 1980; Roth et al. 1980a, 1980b), a brain potential whose relationship to cognitive processing has been repeatedly and powerfully demonstrated (cf. Donchin, Ritter, and McCallum 1978). A second, long-latency, cognitive-related component, slow wave, has also been shown to be reduced in adult schizophrenics relative to normal controls and psychotically depressed patients (Roth et al. 1981). The middle-latency components, N100 and P200, have also been reported to be reduced in schizophrenics (Shagass 1976; Buchsbaum 1977; Lifshitz et al. 1979; Pfefferbaum et al. 1980; Roth et al. 1980a). Since N100 and P200 amplitudes increase with increments in level of attention (e.g., Picton and Hillyard 1974; Hillyard et al. 1978), these data suggest the presence of an attentional dysfunction in the adult schizophrenic. While the endogenous (cognition-related) and exogenous (stimulus-elicted) potentials are reduced in schizophrenics relative to normals, the early brainstem responses do not differ between these groups (Pfefferbaum et al. 1980), indicating that peripheral factors cannot account for the abnormalities that have been reported for the later portions of the schizophrenics’ ERP waveform.

Any one of the ERP differences between schizophrenics and controls may be a consequence of the disturbances in mental functioning produced by the psychosis, rather than a true premorbid indicator. Furthermore, since the various components in the ERP waveform reflect different aspects of information processing, it is to be expected that each might have differential importance as indices of potential psychopathology. Thus, discrepancies that are evident across studies in precisely which components are reduced or enhanced in schizophrenic patients relative to controls should be clarified through the longitudinal following of children at risk for schizophrenia, since the objective of the psychophysiological aspects of this research is to obtain patterns of ERP response that are predictive of the development of the psychosis.

In the behavioral domain, reaction time slowing in schizophrenics relative to controls is one of the most consistently reported findings (cf. Nuechterlein 1977). Since P300 latency and reaction time covary under some conditions (Ritter, Simson, and Vaughan 1972; Kutas, McCarthy, and Donchin 1977; Friedman, Vaughan, and Erlenmeyer-Kimling 1978; Ritter et al. 1979), the reduced amplitude P300 seen in schizophrenics could be due to longer and more variable latency of the single-trial potentials that comprise the averaged response. To determine if this is the case, ERPs and reaction times must be recorded concurrently. Although little used in schizophrenia research, this methodology is powerful as both cognitive deficits and impaired physiological responsiveness have been reported to characterize these disorders. (See, for example, Chapman (1979) for a review of the cognitive area; and Spohn and Patterson (1979) for a review of recent ERP findings.)

This methodology allows the investigator to determine under which circumstances behavioral and physiological measures are or are not related and to what extent deficits in either domain are more severe in acute psychotic states. For example, Roth et al. (1980a) simultaneously recorded ERPs and reaction times in schizophrenics and controls and found reduced P300 amplitude and longer reaction times in the schizophrenics. However, P300 latency was identical in the two groups. Since latency of this component has been associated with stimulus evaluation time (cf. Donchin, Ritter, and McCallum 1978), these data suggested that response organization rather than stimulus evaluation was delayed in the schizophrenics. Several control analyses (reported in Roth et al. 1980b) showed that the reduction in P300 amplitude was not due to the longer and more variable reaction times recorded from the schizophrenics. None of these conclusions could have been reached without concurrent recording of the two measures.

Since cognitive and attentional disturbances are reported to characterize some high-risk children (e.g., Garmezy 1978; MacCrimmon et al. 1980; Cornblatt and Erlenmeyer-Kimling, in press; Erlenmeyer-Kimling et al., in press; Nuechterlein et al., in press), the simultaneous recording of ERPs and behavioral measures could be potentially useful when applied to high-risk samples. However, few studies using this research tactic with high-risk children have been published. We (Friedman, Vaughan, and Erlenmeyer-Kimling 1979) did not find significant mean group differences when visual ERPs were recorded from high-risk and normal control children during two versions of a visual continuous performance test that differed in their
processing complexity. However, of 30 high-risk and 30 normal control subjects, a subgroup of four high-risk children were flagged, who differed from the remainder of the high-risk and normal control groups in showing small, between-task differences in late positive component amplitude. In the normal subjects and the remainder of the high-risk group, the more complex task elicited larger late positivity, indicating that reduced late positive activity may characterize at least some high-risk children.

For the current study, we designed an experiment in which we could record ERPs and behavioral responses simultaneously. The task was a modification of paradigms which had been shown to produce reduced late positive component amplitude in adult schizophrenics relative to controls (e.g., Roth et al. 1980a, 1980b). Its processing requirements ensured that we would record P300 and slow wave (SW), brain potentials thought to reflect cognitive information processing (cf. Donchin, Ritter, and McCallum 1978). Using a task that had produced amplitude differences between adult patients and controls should have maximized our chances of obtaining the same amplitude reduction in children at genetic risk. If we found reduced amplitude late positivity in high-risk children, who do not display any overt symptomatology, this would suggest that the reduction is a true premorbid indicator and not simply a consequence of the disturbances in mental functioning produced by the schizophrenic psychosis.

Methods

Subject Selection and Parental Diagnoses. For this preliminary analysis of the auditory ERP, data are included on the first 56 children (28 high-risk subjects = HR; 28 normal control subjects = NC) from our initial cohort who came for their third round of testing (sample A3) and on the first 30 children (n = 13 HR; 17 NC) from our second cohort (sample B1). Sample B1 provides a replication for sample A. A detailed description of the sample and the study as a whole appears in Erlenmeyer-Kimling et al. (in press).

In both samples, the children of mentally ill parents were ascertained through the admission of the parent to one of several state psychiatric facilities in the New York Metropolitan area. As an initial diagnostic evaluation, records of these patients were reviewed blindly and independently by two psychiatrists. For sample A, each of the reviewers assigned a diagnosis based on the record materials using DSM-II criteria, completed a symptom checklist, and scored the 100-point Global Assessment Scale (Endicott et al. 1976) assessing the severity of impairment. Only those cases for which there was full diagnostic agreement were retained for study. For sample B, in addition, Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1975) were used in the initial diagnostic evaluation.

In sample A, the NC group was obtained with the cooperation of two large school systems. For the purpose of obtaining demographic information on a large number of families, which then formed a pool from which matches (based on socioeconomic level, age, and sex of the children) from the sample B HR subjects could be drawn. In both samples A and B, families were excluded from the NC group if either parent was found to have had psychiatric treatment.

In this preliminary analysis of the data, children of parents with affective psychoses were not included, due to the extremely small number of subjects falling into that category at the time these analyses were performed. Demographic characteristics of the two samples are presented in table 1. In order to be included, all families had to be intact. The age range of subjects from sample A was 11 to 18 and for sample B was 10 to 12.

Task Procedures and Stimuli. The task was designed to obtain ERPs to relevant, irrelevant, and background auditory events. During each block of trials, the children heard three kinds of events: a frequent tone pip (1000 Hz, 64 dB SPL), which occurred 66 percent of the time, a pitch change from the standard frequency (PC at 700 Hz, 64 dB SPL), and a stimulus omission or missing stimulus (MS). PC and MS each occurred 17 percent of the time. The stimuli (50 msec duration, 2.5 msec rise and fall times) were presented binaurally over headphones (TDH-39), with an interstimulus interval of 800 msec. Subjects were instructed to respond with a finger lift (which activated a reaction time key of local design) to one of the infrequent
Table 1. Characteristics of the high-risk and normal control samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>A3</th>
<th></th>
<th>B1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># SM</td>
<td>18</td>
<td>—</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td># SF</td>
<td>5</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td># Both</td>
<td>2</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td># Mixed</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean age</td>
<td>15</td>
<td>14.4</td>
<td>10.8</td>
<td>11.4</td>
</tr>
<tr>
<td>SD</td>
<td>1.7</td>
<td>1.8</td>
<td>.72</td>
<td>.86</td>
</tr>
<tr>
<td># Male</td>
<td>18</td>
<td>16</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td># Female</td>
<td>10</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Totals</td>
<td>28</td>
<td>28</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: SM = schizophrenic mother; SF = schizophrenic father; Both = both parents schizophrenic; Mixed = one parent schizophrenic, one parent affective; HR = high risk; NC = normal control.

Data acquisition and stimulus presentation were under the control of a PDP 11/10 computer, which digitized the physiological data at 4 msec intervals for a 100 msec prestimulus and a 700 msec poststimulus epoch and recorded it, along with reaction time, on nine-track digital tape. Trials containing movement and/or eye artifact were rejected and not included in the averaged responses.

Data Analyses

Averaging. The design of the experiment allowed the averaging across blocks of ERPs to the physically identical stimulus when relevant and when irrelevant, yielding four averages per subject. Ideally, there was a total of 102 PC and MS when relevant and the same number when irrelevant. Eye and other movement artifacts, as well as omission and commission errors (a response to the irrelevant event), reduced these numbers in most subjects. The number of ERP epochs per average varied from 14 to 99 for PC relevant; from 28 to 99 for PC irrelevant; from 12 to 94 for MS relevant; and from 21 to 98 for MS irrelevant. There were no significant differences between HR and NC groups in the number of epochs comprising the averages in either sample A3 or sample B1.

Base to peak measures. For each subject, measures of P350, P400, and SW amplitudes were obtained using the average amplitude over the 100 msec preceding stimulus onset as a baseline. The amplitude measure for each component was computed as the average amplitude over 100 msec centered about the peak of the factor loadings associated with that component and for SW was taken as the average amplitude corresponding to the 100 msec when the SW factor loadings were at their greatest (see below).

Principal components analysis (PCA). ERP components are known to overlap at the scalp. For example, two components with temporally adjacent peaks may summate with a peak latency intermediate to the two original components. This leads to error when attempting to estimate peak amplitude values by visual inspection since the measurement of one component may be contaminated by an unknown contribution from the amplitude of adjacent or overlapping components. PCA has been used quite successfully by ERP investigators to disentangle these overlapping components; see, for example, Donchin and Heffley (1978) for an explanation of PCA in an ERP context. Since P300 and SW are known to interact in this manner (e.g., Squires, Squires, and Hillyard 1975;
Squires et al. 1977; Ruchkin et al. 1980), PCA was used to obtain measures of these potentials uncontaminated by overlap. An added advantage of this method in the study of clinical samples, as in the current report, is that it permits rigorous and objective definitions of components, producing factor score measures of ERP activity without any subjective bias which might occur when hand scoring the data.

The factors which result from the PCA are statistical representations of "peaks" in the original waveforms. A high factor loading indicates a high correlation between the factor and the voltage of the scalp potential at a given point in time. Each factor can then be associated with voltage peaks that are active in different time regions in the original ERP waveforms. The amplitude of each of the peaks in a given subject's waveform can then be expressed using the factor score.

Since amplitude of a given component might distinguish the groups, the cross-products matrix was factored. No transformations are performed on the data when using this association matrix (Glaser and Ruchkin 1976; Donchin and Heffley 1978), thus retaining the original microvolt scale and amplitude information present in each subject's waveform.

Because the factors are statistical representations of components in the original ERPs, it was important to verify that the ERPs from each risk group produced similar factor loading functions and factor structures. This would provide a measure of reliability and allow the pooling of the data across risk groups in order to enter between-groups variance into the analysis. For each of these initial analyses, PCA was performed separately on the ERPs elicited by the PC (relevant and irrelevant) and the MS (relevant and irrelevant) for the NC and HR groups of each sample. Thus, there were 8 PCAs (2 stimuli—MS, PC; by 2 risk groups—HR, NC; by 2 samples—A3, B1). PCA was performed using 66 time points (at 12 msec per point) as "variables" and the waveforms as "cases." For all analyses, the number of cases entered was 2 (relevant/irrelevant) by 4 (electrode locations) by number of subjects, yielding 224 waveforms for the HR and NC groups in sample A3, with 28 subjects per group, and 104 waveforms for the HR subjects of sample B1 (with 13 subjects) and 136 waveforms for the NC group of B1 (with 17 subjects). For the pooled groups PCAs, the number of cases entered was 448 for A3 and 240 for B1.

In order to determine if the factors derived from these separate PCAs of the PC and MS of each risk group and sample represented the same brain activity, the factor scores for each extracted component were subjected to Relevance (relevant/irrelevant) by Electrode location (Fz, Cz, Pz, Oz) ANOVAs with repeated measures on the last two variables. For purposes of the present report, only the results of the P300 and SW factors will be reported.

Statistical significance. Because of the empirically based expectation that only a small percentage of HR children will eventually manifest schizophrenia, it is unlikely that large group differences will occur (see, for example, Hanson, Gottesman, and Heston 1977; Friedman, Frosch, and Erlenmeyer-Kimling 1979). However, it is probable that a small group of deviant subjects could produce a trend toward significance or a marginally significant effect that, if overlooked, would lead to a Type II error (false negative), or the conclusion that parental diagnosis had no effect when, in fact, it did. Therefore, our criterion for statistical significance was set at 0.10.

Results

ERP Waveforms. The grand mean ERPs recorded at the parietal electrode, averaged across subjects within each risk group and sample, to the relevant and irrelevant infrequent events are depicted in figure 1. ERPs associated with the infrequent event contained a large-amplitude late positivity-slow wave complex, which was larger for the relevant than for the irrelevant event. For the PC ERP, this positivity peaks at 350 msec poststimulus and is labeled P350, while for the MS it peaks at 400 msec. These endogenous late positive potentials, although of different latencies, are
The ERPs have been averaged across subjects from each risk group and sample in response to the two infrequent events when relevant and when irrelevant. Arrows denote stimulus onset with time lines every 100 msec. Mean reaction time is indicated by vertical bars with plus and minus one standard deviation marked by horizontal bars. REL = relevant, IRREL = irrelevant; SW = slow wave.

The morphology of the ERPs elicited by both events is remarkably consistent among NC and HR groups of both samples. The most striking difference between HR and NC waveforms occurs when the eliciting event is relevant. The HR subjects of both samples show a reduction in late positivity relative to NC subjects. For A3, this reduction comprises P350, P400, and SW amplitudes, while for B1 it holds only for P350 and P400 amplitudes. For SW, the opposite occurs, greater amplitude for HR than NC subjects of B1 for both PC and MS ERPs.

Mean reaction time (RT) and its associated variability are both greater for the MS than for the PC, but are quite similar when the comparison is made between risk groups of each sample.

**Base to peak measures.** For the PC ERP, P350 amplitude was computed as the average amplitude over 300 to 400 msec poststimulus, and for the MS ERP, P400 amplitude was computed as the average amplitude over 350 to 450 msec poststimulus. For both PC and MS ERP, SW amplitude was computed as the average amplitude over a 100 msec epoch beginning 600 msec after stimulus onset. This corresponded, for both risk groups and samples, to the times when the factors associated with these components had their maximum loadings (see PCA analyses below).

Group (HR/NC) by Relevance (relevant/irrelevant) by Electrode location (Fz, Cz, Pz, Oz) ANOVAs
were performed separately on the PC and MS base to peak measures for each sample, and these results were essentially identical to those using the factor score measures of ERP activity. Therefore, only the results of the ANOVAs using the PCA measures will be reported in detail.

Statistical Representation of the Waveforms. Figure 2 depicts the varimax-rotated factor loading functions obtained from PCAs of the cross-products matrix performed separately on the PC and MS ERPs for each risk group (HR versus NC) and sample (A3 and B1), yielding eight PCAs. With one exception (MS for HR group of sample B1), P300 and SW were always the first two factors extracted. Table 2, which presents the percentages of variance accounted for by each factor, shows that in each analysis the late positivity-SW complex accounted for at least 75 percent of the variance. For the MS, the factor loadings depicted with solid lines have the same shape and peak at approximately the same time as P400 depicted in figure 1. Thus, this factor is associated with P400 in the original data. The second factor, depicted with dashed lines, has high positive loadings in the very late portions of the epoch and is, therefore, associated with SW in the original waveforms. For the pitch change ERPs, the solid-line factors have similar shape and latency to peak as P350 in the original waveforms and are, therefore, associated with that component. As in the MS factors, the dashed lines represent SW activity, since they are active in the very late portion of the recording epoch when P350 is returning to baseline.

Figure 2. Varimax rotated factor loading functions obtained from the within-groups cross-products matrices

The PCAs were performed separately on the PC and MS ERPs within each risk group and sample. Solid lines represent P350 (PC ERP) and P400 (MS ERP) components in the original data, while the dashed lines represent slow wave (SW) activity in the original waveforms. Arrows denote stimulus onset with time lines every 100 ms.
Table 2. Percentage of variance of late positvity–slow wave complex in both groups and samples for within-groups PCAs

<table>
<thead>
<tr>
<th>Sample</th>
<th>PC P350</th>
<th>PC P400</th>
<th>MS P350</th>
<th>MS P400</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 HR</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>B1 NC</td>
<td>59</td>
<td>18</td>
<td>18</td>
<td>68</td>
</tr>
<tr>
<td>A3 HR</td>
<td>61</td>
<td>11</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>A3 NC</td>
<td>62</td>
<td>13</td>
<td>75</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: PC = pitch change ERP; MS = missing stimulus ERP; HR = high risk; NC = normal control.

in the original ERPs.

ANOVA (Relevance by Electrode location) of the factor scores, performed separately for the MS and PC, support the conclusion that the factor associated with late positivity and the factor associated with SW represented the same brain potentials in each of the eight data sets. In all analyses, P350 and P400 factors were both maximal at the parietal electrode, while SW was negative frontally and positive parietally. For all ANOVAs P350 and P400 factors showed main effects of Relevance and Electrode location and strong interactions of Relevance and Electrode location.

Since the components extracted from the separate PCAs were shown to be the same for HR and NC groups of both samples, we pooled the ERP of HR and NC groups (maintaining separateness of each sample), thus allowing between-group variance to enter the PCA. The rotated factor loadings from these analyses appear in figure 3. Again, the late positivity–SW complex accounted for at least

Figure 3. Varimax rotated factor loading functions obtained from the between-groups cross-products matrices

**PITCH CHANGE**

B-1

A-3

**MISSING STIMULUS**

B-1

A-3

P350

P400

SLOW WAVE

SLOW WAVE

800 ms

The PCAs were performed separately on the PC and MS ERPs pooled across risk groups maintaining separateness of the samples. Arrows denote stimulus onset with time lines every 100 msec.
75 percent of the variance (table 3) and, as can be clearly seen, the factors are highly similar to those based on the within-groups analyses.

Factor Score Analyses. The mean factor scores (obtained from the pooled groups analyses) averaged across subjects within each group and sample are presented in figure 4, and the significance of the depicted trends as assessed by Group (HR/NC) by Relevance (relevant/irrelevant) by Electrode location (Fz, Cz, Pz, Oz) ANOVAs are shown in table 4.

Effects not involving risk group. Electrode location was a significant source of variation in all analyses. As can be seen in figure 4, SW was negative frontally and positive at the parietal electrode, as previously reported for this long-latency factor (e.g., Squires, Squires, and Hillyard 1975; Squires et al. 1977), while P350 and P400 showed parietal maxima, also in agreement with previous reports for this late positive activity (e.g., Hillyard et al. 1976; Simson, Vaughan, and Ritter 1977; Friedman, Ritter, and Simson 1978). P350 and P400 produced highly significant Relevance main effects in both samples, with the relevant event producing greater amplitude than the irrelevant event. For these two components, the Relevance by Electrode location interactions were shown by tests for simple effects (Winer 1971) to be due to greater mean differences between relevant and irrelevant at Pz and Oz than at Fz and Cz (all Fs for sample A3 > 3.50, df = 1, 162, p < .10 or less; all Fs sample B1 > 8.00, df = 1, 84, p < .01 or less), and to steeper amplitude gradients across the scalp for relevant than for irrelevant P350 and P400 components (all Fs sample A3 > 5.90, df = 1, 162, p < .05 or less).

Table 3. Percentage of variance of late positivity–slow wave complex in both samples from the between-groups PCAs

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Factor</th>
<th>Sample A3 Percent</th>
<th>Cumulative percent</th>
<th>Sample B1 Percent</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>P350</td>
<td>61</td>
<td>61</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>SW</td>
<td></td>
<td>15</td>
<td>76</td>
<td>16</td>
<td>78</td>
</tr>
<tr>
<td>MS</td>
<td>P400</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>SW</td>
<td></td>
<td>75</td>
<td>85</td>
<td>69</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviations: PC = pitch change; MS = missing stimulus.

Group effects. The factors representing P400 and P350 brain activity showed interactions of Electrode location with Risk Group (with the exception of the PC for sample A3). For the PC ERP, these interactions were due primarily to small, nonsignificant between-group differences at Fz and Cz, with larger, significant differences favoring the NC group at Pz (all Fs sample A3 > 2.60, df = 1, 162, p < .10 or less; all Fs sample B1 > 2.97, df = 1, 84, p < .10 or less). A different pattern was obtained for sample B1’s P400 factor, where the HR group produced significantly greater P400 amplitude than the NC subjects at Fz and Cz (Fs > 3.00, df = 1, 84, p < .10 or less), with no differences at Pz. Reference to figure 4 shows that for SW the significant Electrode location by Group interaction for A3’s PC occurred because the HR group produced SWs which were more negative at the two anterior electrodes than the NC group’s, producing steeper topographic gradients for the HR group’s, with no difference between groups when the MS was irrelevant.

For B1, the significant Relevance by Group interaction for the MS SW occurred because the HR subjects produced greater SW than the NC subjects when the event was relevant (F = 3.9, df = 1, 27, p < .10), with no difference between groups when the MS was irrelevant.

The two significant triple interactions occurred for sample B1 and only for the PC factors. For P350, this interaction was caused by the HR subjects showing significantly greater relevant P350 amplitude at the frontal electrode than the NC group, but significantly less amplitude than the NC group at the parietal electrode (Fs > 5.2, df = 1, 84, p < .05 or less), while for irrelevant P350, the NC subjects showed significantly greater amplitude than the HR subjects, but only at the parietal site (F = 4.06, df = 1, 84, p < .05). For SW, the triple interaction was due to the HR subjects producing significantly greater SW than the NC subjects.
Figure 4. Factor scores obtained from the pooled groups PCAs corresponding to P350, P400, and SW factors depicted in figure 3

Scores have been averaged across subjects in each risk group and sample and are plotted for relevant and irrelevant events at each of the 4 electrode sites (Fz, Cz, Pz, Oz).
Table 4. F ratios from Group by Relevance by Electrode location ANOVAs for samples A and B

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample A3</th>
<th></th>
<th>Sample B1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pitch change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>df</td>
<td>P350</td>
<td>SW</td>
<td>df</td>
</tr>
<tr>
<td>Group (G)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevance (R)</td>
<td>1/54</td>
<td>45.96****</td>
<td>1.20</td>
<td>1/28</td>
</tr>
<tr>
<td>RG</td>
<td>1/54</td>
<td>.91</td>
<td>1.11</td>
<td>1/28</td>
</tr>
<tr>
<td>Electrode location (L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/162</td>
<td>50.20****</td>
<td>39.31****</td>
<td>3/84</td>
</tr>
<tr>
<td>LG</td>
<td>3/162</td>
<td>.81</td>
<td>2.60*</td>
<td>3/84</td>
</tr>
<tr>
<td>RL</td>
<td>3/162</td>
<td>83.71****</td>
<td>8.74****</td>
<td>3/84</td>
</tr>
<tr>
<td>RLG</td>
<td>3/162</td>
<td>1.53</td>
<td>1.13</td>
<td>3/84</td>
</tr>
</tbody>
</table>

|                               | Missing stimulus                |          |                                 |          |
|                               | Factors                         |          |                                 |          |
|                               | df | P400 | SW | df | P400 | SW |          |          |
| Group (G)                     |    |      |    |    |      |    | 1/28     | 1/28     |
| Relevance (R)                 | 1/54 | 30.81**** | 1.80 | 1/28 | 5.99* | .27 |
| RG                            | 1/54 | .96  | .64 | 1/28 | 2.33 | 3.74* |
| Electrode location (L)        |    |      |    |    |      |    |          |          |
|                              | 3/162 | 38.09**** | 26.65**** | 3/84 | 7.03**** | 18.73**** |
| LG                            | 3/162 | 2.40* | .96 | 3/84 | 5.78*** | 1.10 |
| RL                            | 3/162 | 74.52**** | 12.45**** | 3/84 | 32.78**** | 16.31**** |
| RLG                           | 3/162 | 1.54  | .26 | 3/84 | .39  | .85 |

*p < .1/.05; ** p < .01; *** p < .005; **** p < .001.

Analysis of deviant subjects.

We inspected the distributions for P300 and SW at each electrode site for both samples to determine if there were HR subjects at the tails who could have been responsible for producing the small group differences that we observed. While in a few cases (most notably for the SW recorded at the frontal electrode), there were a small number of HR subjects with extreme scores, in the remaining instances it looked as if the majority at all four electrode locations when the PC was relevant ($F_s > 4.00, df = 1, 84, p < .05$ or less), but significantly less SW amplitude when the event was irrelevant, but only at Fz and Cz ($F_s > 5.5, df = 1, 84, p < .025$ or less).
of HR subjects were characterized by the reduced amplitude, leading to the small group effects that we observed.

Analyses of the Behavioral Data. With the exception of reaction time, analyses of behavioral responses were based upon the entire sequence of trials, including those that were rejected for purposes of obtaining artifact-free ERP averages. The number of correct detections of the PC and MS, the number of irrelevant stimuli responded to (i.e., responding to the PC when the MS was relevant), and the number of standards responded to were analyzed with Group (HR/NC) by Stimulus (PC/MS) repeated measures ANOVAs. The MS was the more difficult of the two stimuli to detect; when it was relevant, it produced significantly more errors (misses, responses to the irrelevant event, and responses to the standard) than the PC (all Fs sample A3 > 6.10, df = 1, 54, p < .01 or less; all Fs sample B1 > 11.20, df = 1, 28, p < .002 or less), with the exception of responses to the standard for A3, where no differences between stimuli were noted. For B1, no Group or interaction effects were observed. For A3, there was a significant Group by Stimulus interaction for number of correct responses (F = 4.43, df = 1, 54, p < .04). While the NC group detected the same mean PCs and MSs (mean number of PCs = 86.30, SD = 18; mean number of MSs = 85.40, SD = 11), the HR group detected significantly more PCs than MSs (mean number of PCs = 90.4, SD = 12; mean number of MSs = 79.90, SD = 16) (F = 9.74, df = 1, 54, p < .005), with no differences between the groups.

Reaction times to the relevant events were analyzed in the same manner. Response latency was significantly longer to the MS than the PC in both samples (F sample A3 = 91.00, df = 1, 54, p < .001; F sample B1 = 64.00, df = 1, 28, p < .001), with no Group main or interaction effects. Within-subject reaction time standard deviations were greater to the MS than the PC in both samples (F sample A3 = 84.00, df = 1, 54, p < .01; F sample B1 = 28.64, df = 1, 28, p < .0001), but neither the main effect of Group nor the interaction of Group and Stimulus were significant for either sample.

Discussion

We have shown in two independent samples that late positive activity (P350, P400, and SW) elicited by infrequent, relevant events is significantly reduced in the HR children's waveforms relative to those recorded from normal control subjects. This reduction in late positivity is one of the most consistently reported findings when ERPs are recorded from adult schizophrenics (Levit, Sutton, and Zubin 1973; Shagass 1976; Verleger and Cohen 1978; Timsit-Berthier and Gerono 1979; Pass et al. 1980; Roth et al. 1980b), suggesting that this amplitude reduction may be a premorbid indicator for the development of schizophrenia.

Functional Roles of P300 and SW. Before the various factors that might account for the finding of reduced positivity in the HR s waveforms are discussed, a brief summary of the possible functional role(s) of P300 and SW follows. Although P300 latency can be highly correlated with reaction time, it cannot index the decision to respond, as its peak occurs after that decision has been made (e.g., Ritter, Simson, and Vaughan 1972; Kutas, McCarthy, and Donchin 1977; Friedman, Vaughan, and Erlenmeyer-Kimling 1978; Ritter et al. 1979; Towey et al. 1980). Thus, its functional role has to be related to mental processes (not necessarily conscious) occurring after the discriminative decision. Although the matter is by no means definitively settled, current theorizing and experimental evidence suggest that P300 may reflect processes related to the preparation for future events. These psychological processes may include memory registration, strategy updating, or other, equally likely constructs, and have been referred to collectively as "contextual updating" functions (cf. Donchin, Ritter, and McCallum 1978). The fact that SW amplitude has been enhanced in tasks requiring the subject to engage in strategies that necessitate cognitive processing long after the decision to respond has been made (e.g., Ruchkin et al. 1980) suggests that it too may have a role in the updating process (see also Sutton and Ruchkin 1980). However, this functional interpretation of the P300-SW findings has been inferred from the data; a direct test of the contextual updating hypothesis has not been made. Thus, while still uncertain, it is plausible that the P300-SW complex could reflect brain activity related to these kinds of processes.
factors. Differences in P300 amplitude in averaged ERPs can be due to latency variability in the single trials that comprise the average. Since P300 latency covaries with reaction time under some conditions (e.g., Ritter, Simson, and Vaughan 1972; Kutas, McCarthy, and Donchin 1977; Friedman, Vaughan, and Erlenmeyer-Kimling 1978; Roth, Ford, and Kopell 1978), the reduction seen in the HR children could be due to greater variability in their reaction time distributions, which could indicate greater latency variability in the single trials of these subjects in comparison to the NC subjects. However, the fact that mean reaction time and its associated variability to both infrequent events were quite similar in both groups from both samples mitigates against this explanation.

P300 amplitude could also be reduced by single trial variability which does not covary with reaction time. This source of variation can be assessed using adaptive filtering (Woody 1967), which uses the peak of P300 as the reference point for averaging (the resulting average is referred to as “latency compensated”) (Ruchkin and Sutton 1978). If P300 amplitude is enhanced by the application of the filter, this indicates that latency jitter of P300 in single trials has reduced the amplitude in the conventional, stimulus-locked average. Although it is unlikely that RT-independent variability in P300 latency causes the reduced P300 amplitude in HR subjects, the extent to which latency jitter contributes to this effect should be directly evaluated.

Roth et al. (1980b) eliminated reaction time and latency variability as causative of P300 reduction in their adult schizophrenic sample. P300 amplitude was not normalized either by obtaining averages synchronized with the reaction time response (thus reducing reaction time variability), or by application of the Woody filter (reducing single trial latency variability). Thus, in the adult schizophrenic, P300 is reduced in amplitude in single trials. Together with the reaction time analyses of the current report, these data suggest that P300 reduction in the HR children’s ERPs is also due to amplitude differences occurring in the single trial.

Roth, Ford, and Kopell (1978) and Friedman (1981) have shown that SW grows in amplitude as reaction time and its variability increase. For the A3 HR subjects, SW was significantly reduced compared to the NC children, again arguing against reaction time variability as a determinant of the amplitude loss. However, the B1 HR subjects produced enhanced SW relative to controls, presenting a more complicated picture for this waveform in the two HR samples. Since the B1 HR subjects are younger than those of A3, these SW differences could be due to the age differential between the two samples. In support of this notion, preliminary data (Friedman, unpublished observations) demonstrate larger SW in the ERPs of the youngest subjects tested.

**P300 Reduction—Subjective Probability and Task Relevance.** The usual interpretation of smaller P300s is that the stimuli that elicited them were less task relevant or had a higher subjective probability or expectancy (e.g., Duncan-Johnson and Donchin 1977; Roth et al. 1976; Squires et al. 1976; Johnson and Donchin 1980). Since RT was similar in both groups, it would be difficult to consider the reduced amplitude as indicating that the infrequent stimuli were treated as less task relevant by the HR than by the NC subjects. It seems more likely that the deficit lies in not perceiving the probabilities accurately. There is a systematic increase in P300-SW amplitude elicited by an event depending upon the number of repetitions of a different event that preceded it (Squires et al. 1976; Johnson and Donchin 1980). If some HR subjects do not form accurate representations of the sequential probability of the stimulus train, this might be one way in which P300 amplitude is reduced in these subjects.

Certainly, cognitive and/or attentional disturbances, which have been reported to characterize some high-risk children (e.g., Asarnow et al. 1977; Rutschmann, Cornblatt, and Erlenmeyer-Kimling 1977; Garmezy 1978; MacCrimmon et al. 1980; Cornblatt and Erlenmeyer-Kimling, in press; Erlenmeyer-Kimling et al., in press; Nuechterlein et al., in press), could lead to dysfunctions in expectancy formation. As Roth (1977) has pointed out, it is likely that task relevance and subjective probability interact, in that subjects with attentional deficits may not form accurate representations of stimulus occurrence or may not accurately perceive the probability structure of the stimulus sequence. However, when ERPs are averaged according to the sequence of stimuli that preceded the eliciting stimulus, adult schizophrenics produce sequential dependencies whose P300 amplitude and reaction time distributions are similar.
to those of normal controls, although the schizophrenics show overall reduced P300 amplitude and reaction time slowing relative to the normal controls (Duncan-Johnson, Roth, and Kopell, in press). Thus, the reduced P300 amplitude seen with adult schizophrenics does not seem to be due to an inaccurate perception of the probability structure of the stimulus train.

In a similar vein, it is doubtful that inattention accounts for our results since, if HR subjects were not as attentive as NC subjects, we would expect differences in performance measures between the groups. Neither mean RT and its associated variability nor any of the error rate measures of performance significantly discriminated HR from NC subjects. It is more probable that the reduced P300 amplitudes found in HR children are due to a defect in the basic cognitive mechanisms that are indexed by these late positive waveforms and may reflect dysfunctions in the neural structures responsible for their generation.

**Diagnostic Specificity of P300 Reduction in Children.** Children at risk for schizophrenia are not the only subjects who show reduced P300 amplitude. Both Prichep, Sutton, and Hakerem (1976) and Klorman et al. (1979) have reported reduced P300 amplitude in hyperkinetic compared with normal control children in a guessing paradigm (Prichep et al.) and a version of the continuous performance test (Klorman et al.). Prichep et al. (1976) reported that the hyperkinetic children's waveforms were characterized by reduced positivity which began with a negative component at 250 msec poststimulus and extended to the end of the recording epoch. This reduction in positivity appeared to reflect the marked attentional deficits which these children exhibited, as methylphenidate normalized their ERPs in both studies. It is difficult to determine whether the reduction seen in the HR children is qualitatively different from that seen in hyperkinetic children. Behavioral evidence suggestive of a qualitative difference has been presented by Nuechterlein et al. (in press), who found reduced d' (a measure of sensitivity) in HR compared with NC subjects, whereas beta or response caution decrements characterized the hyperkinetic subjects. This performance deficit is consistent with the impulsive style of such children, a style not reported for HR subjects (e.g., Hanson, Gottesman, and Heston 1976; MacCrimmon et al. 1980; Erlenmeyer-Kimling et al., in press; Nuechterlein et al., in press). Novick and her associates (Novick, Kurtzberg, and Vaughan 1979; Novick et al. 1980) have also reported reduced P300 amplitudes in autistic relative to age-matched normal control children, whether elicited by changes in pitch or stimulus omissions (in both visual and auditory modalities). Control analyses enabled these investigators to eliminate RT variability as a cause of the reduced late positivity. The clinical symptom patterns and behavioral disturbances seen in hyperkinetic and autistic children are distinctly different and much more severe than those seen in HR children. However, the finding of reduced late positive activity in all three groups of children may reflect certain common pathophysiological mechanisms in the brain systems that underlie the generation of the cognitive ERPs.

**Deviant Subjects.** The fact that we restricted our analyses only to the late components (P300 and SW) and did not look at any of the earlier negative or positive waves (e.g., N100, P200, and N250) may have limited our chances of detecting outliers. Since HR children have been characterized as displaying attentional deficits, it is likely that the "vulnerable" children in the sample would exhibit a pattern of ERP response characterized by deficiencies in the earlier negativities—for example, in the N100 component or in the slow negative shift, Nd, which may underlie the N100 amplitude modulations seen in selective attention tasks (Naatanen and Michie 1979; Hansen and Hillyard 1980). However, our paradigm cannot provide evidence for deficits in selective attention, since we had no ERP index of attention to an "unattended" channel, as do the investigators using dichotic listening paradigms. It is likely, therefore, that the pattern of latency shifts and amplitude modulations of all the ERP components seen in these paradigms will have to be used to define deviant subgroups, as it is unlikely, on the basis of behavioral dysfunctions shown by HR children, that deviations in a single component will define a vulnerable individual.

From a genetic viewpoint, different models of transmission may lead to different expectations regarding whether one would expect to obtain group differences or a sharply distinct subgroup of deviant individuals. Additionally, under a multifactorial threshold model, it is possible to conceive of a
situation in which some indicators may be under the control of genes having a large, major effect—suggesting that sharp outlier differences might emerge—while other indicators are themselves determined by a complex of genes such that a more generalized group difference would result. These factors aside, the small numbers of subjects in these preliminary analyses also made it less likely, on a statistical basis, for us to have detected a subgroup of significantly deviant subjects.

Conclusions

While it is currently difficult to define precisely the cause of late positive amplitude reduction in HR individuals, this pattern of ERP response, coupled with the cognitive and attentional disturbances thus far reported, is suggestive of a fundamental deficit in HR children as discussed by Garmezy (1978). The results also highlight the importance of using a paradigm that has successfully discriminated adult patients from controls, since other ERP paradigms we have used (Friedman, Vaughan, and Erlenmeyer-Kimling 1979) have not produced significant group differences. Furthermore, finding this reduction in children at risk, who have not yet become schizophrenic, suggests that reduced P300 may be a “vulnerability marker,” or an enduring trait, rather than an “episode marker” indicative of a transient state (cf. Zubin and Spring 1977). Our next step will be to determine the pattern of behavioral responses and clinical status of each of the children in the HR group in order to compare these measures with our ERP indices. Our goal is to determine if a profile of measures from these different domains, which deviates from the normal, characterizes some of the HR children, as they may be the most vulnerable in the HR group.

References


Johnson, R., Jr., and Donchin, E. P300 and stimulus categorization: Two plus one is not so different from one plus one. *Psychophysiology*, 17:167-178, 1980.


Pass, H.L.; Klorman, R.; Salzman, L.F.; Klein, R.H.; and Kaskey,


Sutton, S., and Ruchkin, D.S. "Positive Slow Wave and P300:..."
Differences and Similarities in
Their Relationships to Behavioral
Variables." Presented at the Con-
ference on EEG Correlates of In-
formation Processing, Zeist, Hol-
land, December 1980.

Timsit-Berthier, M., and Gerono,
A. Late components of the audito-
ry evoked response in schizo-
phrenics. (Abstract) In: Lehmann,
D., and Callaway, E., eds. Event-
Related Potentials in Man: Applica-
tions and Problems. New York: Ple-

Towey, J.; Rist, F.; Hakerem, G.;
Ruchkin, D.S.; and Sutton, S.
N250 latency and decision time.
Bulletin of the Psychonomic Society,

Venables, P.H. The electrodermal
psychophysiology of schizophre-
nics and children at risk for schizo-
phrenia: Controversies and devel-
opments. Schizophrenia Bulle-

Verleger, R., and Cohen, R. Ef-
facts of certainty, modality shift,
and guess outcome on evoked po-
tentials and reaction times in
chronic schizophrenics. Psycholog-
ical Medicine, 8:81–93, 1978.

Winer, B.J. Statistical Principles in
Experimental Design. New York:

Woody, C.D. Characterization of
an adaptive filter for the analysis
of variable latency neuroelectric
signals. Medical & Biological Engi-

Zahn, T.P. Autonomic nervous
system characteristics possibly re-
lated to a genetic predisposition to
schizophrenia. Schizophrenia Bulle-

Zerbin-Rudin, E. Endogene

Zubin, J., and Spring, B. Vul
nerability—A new view of
schizophrenia. Journal of Abnormal

Acknowledgments
The authors would like to express
their gratitude to the following
people for their aid in this project:
Mr. Joseph Gallichio and Mr.
Charles Brown III for aid with data
analysis; Mr. James Hollenberg
and Ms. Henrietta Wolland for
computer programming; Drs. Wal-
ter Ritter, Walton Roth, and Sam-
uel Sutton for reading an earlier
version of this manuscript and for
making many useful suggestions
and criticisms; Ms. Noreen Dodge,
Ms. Anne Moscato, and Ms. Robin
Cano for secretarial assistance; we
thank the children who were the
subjects of this study and their
parents for giving their time in or-
der to participate in this project.
This work was supported by grant
MH–19560 from the USPHS and
by the New York State Department
of Mental Hygiene.

The Authors
David Friedman, Ph.D., is Associate
Research Scientist, Department
of Medical Genetics, New York
State Psychiatric Institute, and As-
sistant Professor of Clinical Psych-
iatry, Department of Psychiatry,
Columbia University Medical Cen-
ter, New York, NY. Herbert
Vaughan, Jr., M.D., is Professor of
Neurosciences and Neurology, De-
partments of Neuroscience and Neurology, and the Rose F.
Kennedy Center for Research in
Mental Retardation and Human
Development, Albert Einstein
College of Medicine, Bronx, NY.
L. Erlenmeyer-Kimling, Ph.D., is
Principal Research Scientist and
Director of the Division of Devel-
opmental Behavioral Studies, De-
partment of Medical Genetics,
New York State Psychiatric Insti-
tute, and Professor, Department of
Psychiatry, Columbia University
Medical Center, New York, NY.