Event-Related Potentials (ERPs) as Indicators of Risk for Schizophrenia

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Abstract
Evidence is reviewed concerning the viability of cognitive event-related potential (ERP) indices to serve as psychophysiological markers for liability to schizophrenia and schizophrenia-related disorders. Methodologic problems that hinder the establishment of ERPs as such markers are also detailed. The ERP data from prospective high-risk and family-transmission paradigms were subjected to criteria that have been used to establish the marker status of a psychobiological variable. It is concluded that (1) there is a clear need for more studies of ERP component stability and of transmission of ERP parameters within normal families; (2) multiple tasks (in addition to the oddball experiment) must be used to probe the range of information-processing deficits in the schizophrenic syndrome; (3) investigators should pay greater attention to the scalp distribution of ERP components; and (4) profiles of multiple ERP indices may be required to enhance the probability of achieving diagnostic specificity.


In recent years, event-related brain potentials have increasingly been used as putative biological "markers" or indicators of liability to mental illnesses such as schizophrenia and major depressive disorder (for a general overview, see Pritchard 1986; for an overview of psychobiological markers as used in the high-risk design, see Friedman 1991). For an overview of the ERP technique and methods by which ERPs have been related to cognitive phenomena, the reader is referred to Hillyard and Picton (1987). We will first consider some of the methodologic problems that confront the researcher attempting to establish ERPs as putative markers, and then we will briefly review the findings of studies of adult schizophrenia patients. Then we will review ERP vulnerability indicators in samples at risk. We will end with a summary of ERP vulnerability criteria and directions for future research.

The Event-Related Brain Potential (ERP)

ERP voltage swings, or components (figure 1), have typically been categorized as either exogenous or endogenous. The earlier components, such as N100 and P200, are thought to be primarily exogenous because they are affected more by the physical parameters of the stimulus. The later (N200, P3—or P3b—and slow wave) components are thought to be primarily endogenous because they are affected more by the physical parameters of the stimulus. The later (N200, P3—or P3b—and slow wave) components are thought to be primarily endogenous because they can be elicited even in the absence of stimulation and their amplitude and latency can be modulated in relation to the role or meaning of the stimulus as defined by the task or as perceived by the subject (cf. Sutton et al. 1965; Donchin et al. 1978). The ERP technique provides a safe, noninvasive approach to the study of psychophysiological correlates of human mental processes. Compared with other methods that
provide images of brain function, such as positron emission tomography, ERP methodology is inexpensive to implement. Moreover, it provides a much finer temporal resolution than most other currently available techniques, although its spatial resolution (i.e., the ability to localize the sources of electrical events within the brain) is not as exact as that of these other methods. However, recently developed source localization techniques (e.g., Scherg 1990) may allow inferences as to likely intracranial generators of ERP phenomena.

The scalp distribution, or topography, of a component is important in the interpretation of its functional significance. In typical experiments, recordings are obtained from at least three or four midline electrodes placed at frontal (labeled Fz), central (labeled Cz), parietal (labeled Pz), and occipital (labeled O2) scalp sites. Scalp distribution refers to the fact that the amplitude of a particular component has a characteristic distribution of amplitudes across these three (or more) scalp electrode sites. For example, as can be seen in figure 2, the component labeled P3a displays its largest amplitudes between the Cz and Pz scalp leads, whereas the longer latency component labeled P3b shows a distinct focus at the parietal electrode site. This difference in scalp distribution is typically interpreted as indicating a difference in the site of intracranial generation (although one cannot infer where in the brain these events are generated from inspection of the scalp distribution alone). Furthermore, it also suggests that the putative functional roles of these two components may differ (see section on "Methodologic Issues"). This topographic-functional relationship is important with respect to ERPs and schizophrenia, as there are well-documented differences in scalp distribution among the cogni-
tive components that could have implications for the cognitive mechanisms that are altered in schizophrenia. These are discussed below.

The vast majority of investigators using the ERP as a putative biological marker for the liability to mental illness have concentrated their efforts on the study of the P3b component. Throughout this review, the terms P3 and P3b will be used interchangeably to refer to the classical P3 component (cf. Donchin et al. 1978) that is typically recorded with a parietal maximum scalp distribution (in a midline series of scalp electrodes) and elicited by the detection of task-relevant events. The P3b component stands in contrast to P3 components that have more anteriorly oriented scalp distributions, such as P3a (see below) or the “novelty P3,” elicited by unexpected “novel” stimuli (Courchesne 1983). The P3b component can have a latency to peak of anywhere from 300 to 1,000 ms, depending on the requirements of the task. The P3b component is exquisitely sensitive to task demands and therefore should not be confused with a biological assay.

Methodologic Issues

In many of the investigations reviewed below, ERPs were recorded from only a single central (or vertex) placement on the scalp midline. However, within the past 10 years it has become increasingly clear that there are several P3bs, which differ with respect to the distribution of amplitudes along the scalp midline (and along the lateral scalp overlying the two hemispheres). These differences in scalp distribution depend on the complexity of the task and stimulus parameters (see Johnson 1993 for a detailed treatment of these issues). Thus, differentiating these different P3b components requires at least three or four midline electrode sites, a necessity that has consequences for the study of schizophrenia. Since different P3bs have different putative cognitive correlates (see, e.g., Ruchkin et al. 1990), the interpretation one makes of the cognitive deficit exhibited by the schizophrenia sample in question depends on the scalp distribution and cognitive correlates of the particular P3b one has recorded. Another consequence of recording from a single scalp placement is that differences in scalp distribution between patient and control samples cannot be assessed. Since differences in scalp distribution imply differences in the site of intracranial generation, the use of only one electrode ignores a potentially illuminating means of differentiating patient and control groups.

In 1975, Squires et al. recorded what they termed a “P3a,” with maximum amplitude at the Cz or vertex scalp site and a peak latency of about 280 ms during a passive oddball paradigm (i.e., the subject read a book while a series of frequent and infrequent tones was presented in the background). This component was elicited by the highly infrequent stimuli, even though those stimuli were “unattended.” In contrast, the classical P3 component—in Squires et al.’s terminology, the “P3b”—was recorded with maximum amplitude at the midline parietal scalp site in response to infrequent target stimuli that required a task-relevant response. This P3b component occurred with a considerably longer latency to peak than the P3a, which was also seen in the ERP elicited by the infrequent, task-relevant target. A hypothetical example of ERPs recorded in this paradigm is depicted in figure 2. Note that in the figure, as described above, P3a and P3b display different distributions of amplitudes across the three electrode sites, but they occur with similar amplitudes at the central (i.e., Cz) electrode site. This similarity makes it difficult to know with certainty, in those studies employing only a single Cz electrode placement and reporting fairly short-latency P3s to target stimuli, whether the component in question was the P3a or the longer latency P3b. Furthermore, since P3a and P3b differ with respect to putative functional correlates (see Squires et al. 1975), the uncertainty as to which P3 component was measured has the effect of obscuring the cognitive mechanism that may or may not be deficient in the schizophrenic sample.

Another critical issue in the study of psychiatric patients is the need to control for age. For example, P3b amplitude decreases and its latency increases as a function of increasing age (e.g., Pfefferbaum et al. 1984). Thus, if schizophrenic and control groups differ with respect to this variable, between-group amplitude and latency indices will be confounded by age differences (for an example, see section on “Family studies of psychiatric patients”).

ERP Indices as Putative Biological Markers

In this overview, we have limited our discussion primarily to studies published after 1986, since thor-
though reviews exist for data published before that date (e.g., Pritchard 1986). We will focus here on only those investigations that have tested biological relatives of mentally ill probands, that is, either children at risk as defined by their parents’ diagnoses or adult relatives of probands with schizophrenia or with related spectrum disorders. Before critically reviewing the ERP findings in samples of at-risk persons, we will first provide a brief review of the major ERP findings in adult schizophrenia patients, as these have provided the impetus for studies of children at risk and for the more recent investigations using the family or genetic study method. We will then briefly review some of the criteria for the identification of a marker. Throughout this overview, we will attempt to determine whether the results of the studies cited do or do not support ERP components as potential biological markers.

**Brief Review of ERP Findings in Adult Schizophrenia Patients.**

**P3b.** By far the most robust finding is that of reduced amplitude of P3b in schizophrenic (relative to control) samples. However, this finding is not specific with respect to the diagnosis of schizophrenia, as it is also found in a number of other disorders (see section on “Diagnostic Specificity”). P3b reduction in schizophrenic samples has been reported most often in studies using the oddball paradigm, in which a frequent tone (or other event) is randomly replaced by an infrequent event, which the subject must either count or overtly respond to (i.e., with a timed motor response). Since P3b amplitude reduction was originally reported by Roth and Cannon (1972), it has been replicated numerous times with both auditory (e.g., Pfefferbaum et al. 1990) and visual (e.g., Pass et al. 1980) stimuli.

The more controversial finding of a reduction in P3b amplitude over the left, relative to the right, temporal scalp in schizophrenia subjects compared with normal control subjects was originally reported by Morstyn et al. (1983) and was subsequently replicated by investigators within the same laboratory (Faux et al. 1990). However, at least two investigative teams (Pfefferbaum et al. 1990; Moore et al. 1992) have not found this asymmetry, so the robustness of this phenomenon remains to be established.

In a preliminary study, Duncan et al. (1987b) studied 14 medicated schizophrenia patients and 10 normal control subjects, using both visual and auditory oddball paradigms. P3b amplitude in the schizophrenia sample was reduced relative to amplitude in the control sample, in the auditory but not the visual modality. These findings suggest that P3b elicited by auditory stimuli might serve as a trait marker for the liability to the disorder. However, Duncan et al. had no comparison psychiatric group with which to assess the specificity of the finding to more clearly determine its potential as a diagnostically specific candidate marker.

Consistent with their between-modality study (Duncan et al. 1987b), Duncan et al. (1987a) presented preliminary data suggesting that P3b amplitude in the visual modality might serve as a state marker for cognitive dysfunction secondary to the presence of clinical symptoms. In that study, P3b amplitude was larger in asymptomatic medicated schizophrenia patients than in the same patients when unmedicated in the acute phase of the illness. This kind of longitudinal study is sorely needed but is obviously difficult to implement. Data from such a study would go a long way toward establishing one of the criteria for marker candidacy—presence during the acute and remitted stages of the illness.

**N100 and processing negativity.** A negative component peaking at about 100 ms following auditory stimuli (i.e., N100) is also reduced in the schizophrenia patient’s ERP (Roth et al. 1980). This reduction does not appear to be specific to schizophrenia, as it is also found in patients with major depressive disorder. Interestingly, from the figure presented in the Duncan et al. (1987b) article reviewed above, it appears that N100 was reduced in the schizophrenia sample in the auditory but not the visual modality. However, the significance of this effect was not assessed.

The reduction in N100 might be the result of an overlapping component, the “processing negativity” (see figure 1; see Naatanen 1982 for a review), that is elicited during selective attention paradigms and appears to be reduced in schizophrenia patients (e.g., Baribeau-Braun et al. 1983, Michie et al. 1990). This component is larger in response to stimuli in an “attended” than in an “unattended” channel. Since deficits in selective attention have been proposed to account for some schizophrenic symptomatology (e.g., Garmezy 1977), a reduction in processing negativity is consistent with this kind of cognitive dysfunction. However, there are few studies that were specifically de-
signed to elicit this electrical activity in individuals at risk for schizophrenia (see Schreiber et al. 1991 for an example).

Mismatch negativity. Another possibility is that the deficit(s) reflected in reduced P3b and processing negativity amplitudes (assumed to index controlled attentional and cognitive mechanisms) may be due to dysfunction in a preattentive, relatively automatic mechanism reflected in the mismatch negativity (Shelley et al. 1991a). The mismatch negativity is an ERP component elicited by infrequent “oddball” stimuli. It can be observed most clearly by subtracting the frequent ERP from the infrequent ERP recorded during versions of the oddball paradigm. It is typically recorded when subjects are asked to pay attention to stimuli delivered as part of a primary task while the frequent and infrequent auditory stimuli, which subjects are instructed to ignore, are presented in the background.

In one of the two studies of this component, Shelley et al. (1991a) recorded mismatch negativity in 11 medicated schizophrenia patients and 11 age- and gender-matched control subjects. The mismatch negativity (recorded at a mean latency of about 200 ms in patients and control subjects) was smaller in the schizophrenic sample than in the control sample. This result has recently been replicated in unmedicated schizophrenia patients (Catts et al. 1992). Shelley et al. (1991a) concluded that what they termed deficits in “controlled attention” (as indexed by reductions in P3b and processing negativity amplitudes) might be due, in part, to deficits in preattentive processing. Their results are intriguing and in need of followup, especially since they did not have a psychiatric control group with which to assess the diagnostic specificity of the finding.

Slow wave. A longer latency ERP component that has been studied in the adult schizophrenia patient is the slow wave (see figures 1 and 2). This component is also elicited by stimuli in the oddball paradigm. It has a characteristic scalp distribution—negative amplitude at the anterior regions of the scalp and positive amplitude at posterior scalp leads. Little systematic research exists on the slow wave in schizophrenic samples, although Roth et al. (1981) reported that the slow wave was reduced in their schizophrenic sample.

P50. A much earlier deflection elicited by auditory stimuli at about 50 ms poststimulus, the P50, has received a good deal of attention in recent years as a putative marker for schizophrenia (see Freedman et al. 1987). The paradigm that has most often been used in schizophrenia research to elicit P50 has been the conditioning-test manipulation. Two auditory stimuli are presented, typically 500 ms apart, and the amount of reduction (usually expressed as a ratio) in P50 amplitude to the second (or test) stimulus relative to the amplitude of the first (or conditioning) stimulus is taken as the measure of P50 suppression.

Adler et al. (1982) reported that P50 to the test stimulus was less suppressed in schizophrenia subjects than in normal subjects. The investigators interpreted this as indicating a defective “gating” or “filtering” mechanism in schizophrenia. However, as noted by Naber et al. (1992), an alternative interpretation in terms of neuronal recovery cycle or refractory period (e.g., Erwin and Buchwald 1986) is also possible. The latter interpretation does not require the anchoring of P50 suppression in the functional, behavioral domain of gating or defective filtering. Subsequent reports (e.g., Siegel et al. 1984) suggested familial transmission in families with schizophrenia probands. The difference in P50 suppression between schizophrenia and normal subjects has been reproduced several times by the Colorado group (e.g., Adler et al. 1982; Freedman et al. 1987) and has recently been replicated by an independent laboratory (Judd et al. 1992). However, there have been reports of failure to find strong P50 suppression in normal subjects, with a concomitant lack of schizophrenic-normal differences in P50 suppression (Kathmann and Engel 1990), and of only partial evidence for its suppression in schizophrenia subjects (Deldin et al. 1991). The differences in the rate of suppression between Kathmann and Engel’s (1990) study and the Colorado group’s studies could not be explained by a variety of factors (Naber et al. 1992).

More recently, the reliability—an important criterion in determining a measure’s potential as a putative marker (see section on “Overview of Criteria for a Vulnerability Indicator”—of the ratio measure of P50 suppression has been seriously questioned (Boutros et al. 1991). Thus, the status of P50 suppression as a putative marker for schizophrenia remains uncertain until these discrepancies can be understood and the differences between studies reconciled.

Overview of Criteria for a Vulnerability Indicator. Vulnerability indicators have been invoked to aid in the identification and reso-
lution of heritable components that have been hypothesized to underlie the expression of disorder (Rieder and Gershon 1978). It is proposed that such indicators are closer to gene action, and hence more penetrant (more likely to be expressed) than the psychiatric disorder itself, whose expression depends on (the necessary but insufficient) genetic vulnerability plus eliciting events (which may include independent constitutional and environmental insults—Gottesman and Shields 1982; Gottesman and Bertelsen 1989). Desirable properties of vulnerability indicators include longitudinal stability, sensitivity, and specificity of expression with respect to the target disorder, and a relative insensitivity with respect to covariates such as age, gender, medication and clinical state effects (Spring and Zubin 1978; Iacono 1985; Baron 1986; Erlenmeyer-Kimling 1987). Although vulnerability indicators are presumed to reflect heritable processes, evidence of genetic determinants is required. This kind of evidence has been sought by investigators using designs such as family and twin studies. Relevant ERP evidence is reviewed below.

Measurement Issues.

Stability of ERP indices.

Measurements of some ERP components do appear to satisfy the stability criteria for normal populations (Polich 1986; Shelley et al. 1991b). For P3b, amplitude appears to be more reliably measured than latency when measurements are based on the averaged ERP (Fabiani et al. 1987). However, a substantial increase in P3b latency reliability can be obtained by using measurements based on the single-trial, rather than the averaged, ERP (Fabiani et al. 1987). Nevertheless, because of the small number of studies and the small number of time periods sampled (no more than two), there is a clear need for additional normative studies over longer periods of time.

Family aggregation. The literature dealing with the heritability of ERP components is quite small, but, in general, it is consistent with the notion that at least some ERP characteristics may be under genetic control (e.g., Bock 1976; Polich and Burns 1987). However, to our knowledge, there are no studies of ERP component transmission in normal families. This gap must be filled because when studying indicators of risk one is interested in characteristics that are presumably transmitted within families.

ERP Indices in Subjects at Risk for Schizophrenia.

Prospective studies. Findings through 1986 have been summarized by Pritchard (1986) and findings through 1988 by Friedman (1991). Since 1988, there have been three additional studies of children at risk (Schreiber et al. 1989, 1991, in press).

Schreiber et al. (1989, 1991) reported that N2 and P3b latencies were prolonged in children at risk for schizophrenia relative to age-, sex-, and education-matched control subjects when the components were elicited by infrequent tone pips during an oddball experiment. There were no between-group differences for ERP amplitude. However, there was no psychiatric control group with which to assess the specificity of the latency findings to children at risk for schizophrenia. The lack of a psychiatric control group detracts from the forcefulness of the conclusion that prolonged latency of the endogenous ERP components characterizes children at risk for schizophrenia and could, therefore, serve as a marker for liability to the illness.

Schreiber et al. (in press), employing the selective-attention paradigm, compared the amplitude of the processing negativity in children at risk for schizophrenia with its amplitude in age-, sex- and education-matched control subjects. Schreiber et al.'s findings were similar to findings with adult schizophrenia patients—the processing negativity was reduced in the high-risk children relative to control subjects, indicating a deficit in selective attention in these subjects. Again, although this is an intriguing and potentially important finding, the specificity of the result to the development of schizophrenia is equivocal because of the lack of a psychiatric control group.

Squires-Wheeler et al. (1993) examined the relationship between P3b amplitudes recorded in adolescents as part of the New York High-Risk Project (detailed in Friedman et al. 1986, 1988) and subsequent clinical assessments obtained when the same adolescents had become young adults. The expectation (based on the adult literature) was that a specific link would be found between reduced P3b amplitudes recorded in adolescence and subsequent schizophrenia-spectrum clinical status in young adulthood in subjects with psychiatrically ill parents. Such a link was not observed.

To summarize, there is little evidence from the few high-risk studies available that ERPs can predict the specific diagnosis of schizophrenia or schizophrenia-related disorders for individuals within high-risk samples. Thus, the results...
of these studies fail to satisfy one of the major criteria for the presence of a biological marker. However, this should not be stated as a strong conclusion because it is based on small numbers of subjects within the New York and German high-risk samples (i.e., the Schreiber et al. studies).

**Family studies of psychiatric patients.** Condray et al. (in press) assessed electrophysiological, neuropsychological, and behavioral functioning in a monozygotic (Mz) twin concordant for schizophrenia. The clinical history of the twins differed markedly: the index twin had had five episodes since his first (at age 19), with the last occurring 9 months before testing, whereas the cotwin had experienced only one episode since his first (at age 20), and that occurrence was 15 years before testing. Nonetheless, this twin study (although only one “case”) appears to be a good model for testing the validity of some of the criteria established for assessing ERP indices as potential markers for the liability to schizophrenia. P3b amplitude elicited by infrequent auditory stimuli in the oddball paradigm did not differ between the twins. However, P3b latency was markedly longer in the ERPs of the index twin (432 and 448 ms, respectively, for count vs. respond conditions) than in those of the cotwin, for whom P3b latency was in the normal range (352 ms for both conditions). This latency difference is not consistent with previous reports of highly similar P3b latencies in Mz twins (e.g., Polich and Burns 1987) and suggests that in this case P3b latency is not a marker for liability to schizophrenia.

Kidogami et al. (1992) recorded P3bs during a version of the oddball paradigm in schizophrenia patients, relatives of schizophrenia probands, and normal control subjects. Consistent with previous reports, P3b amplitude was reduced in the schizophrenic sample relative to the control sample. However, it was also reduced in the family-member sample relative to the control sample. On this basis, the investigators concluded that P3b amplitude reduction could serve as a trait marker for schizophrenia. However, two methodologic problems temper this conclusion: (1) the family members were related to schizophrenia probands, but not to those probands who were the subjects of the study; and (2) the family-member group was older (mean age = 61.8 yr, standard deviation [SD] = 13.4) than the normal control group (mean age = 43.5 yr, SD = 13.4) and the schizophrenia patient group (mean age = 51.8 yr, SD = 5.9). Thus, the amplitude reduction seen in the family-member group may simply have been due to the fact that this group was older than either of the other two groups.

In another family study, Blackwood et al. (1991b) studied P3b and eye tracking abnormalities in family members from 20 high-density schizophrenia families and 212 normal control subjects. The P3s were elicited during a version of the auditory oddball paradigm. As expected, P3 amplitude reduction and latency prolongation characterized the schizophrenia proband sample. The distributions of P3 latency were bimodal in the family samples, with approximately half of nonschizophrenia relatives showing prolonged P3 latency. Of 41 family members who showed prolonged P3 latency, 18 had been diagnosed with major psychiatric disorders, while 19 had no history of such disorders. P3 latency prolongation was not observed in many of the schizophrenia probands, which suggests a lack of sensitivity for schizophrenic disorder. P3 amplitude reduction, in contrast, was not prevalent in the family sample. Although this was an important study in attempting to establish P3 as a biological marker, several caveats are in order. First, a single vertex electrode site was used, which makes it difficult (as mentioned above) to determine which P3 component was recorded. Second, the P3 latency values were not age-adjusted. This is especially germane to the diagnostic breakdowns in the family sample, as it would be important to know the age distribution of those showing the abnormally prolonged P3 latencies (since the parents of the probands are older). Finally, although Blackwood et al. (1991b) cannot be faulted for failing to study normal families in the same fashion as schizophrenia families, normal families would be extremely important sources of control data.

In an extension of this methodology, Blackwood et al. (1991a) studied deoxyribonucleic acid (DNA) markers and P3 responses in previously studied high-density schizophrenia families. Among a number of definitions of the “affected phenotype,” Blackwood et al. (1991a) used expression of P3 latency prolongation as the only phenotypic expression of the putative genotype. This affected phenotype model (as well as other, more clinically defined models) resulted in negative lod scores for linkage to the q11–13 region of chromosome 5, thus failing to confirm the findings of...
in the schizotypal relatives of the probands. Either latency prolongation or amplitude reduction of P3b should have been present in at least some of the schizotypal individuals that have relatives with schizophrenia, since schizophrenia-spectrum disorders are hypothesized to share genetic variance with schizophrenia (e.g., Gunderson and Siever 1985).

**Diagnostic Specificity.** P3b amplitude decrement occurs in a host of disorders that do not appear to have a common pathophysiology (dementia, Pfefferbaum et al. 1984; alcoholism, Porjesz et al. 1980; major depression, Diner et al. 1985). Similarly, in the family studies reported by Blackwood et al. (1991a, 1991b), there is evidence for nonspecificity of P3b latency prolongation within the same family—that is, prolonged latency was exhibited by family members diagnosed with schizophrenia as well as by those diagnosed with bipolar disorder and major depressive disorder.

It is not known whether the processing negativity and mismatch negativity are diagnostically specific, as the studies designed to elicit these ERP phenomena (e.g., Bariabeau-Braun et al. 1983; Michie et al. 1990; Shelley et al. 1991a) did not include psychiatric control groups in their designs.

**Do the ERP Findings Satisfy Vulnerability Criteria?**

**Low population prevalence.** It will be necessary to standardize the definition of "reduced amplitude" and "prolonged latency" of ERP components to determine a common threshold for comparison between studies and to determine population rates. One approach is to use SD units, but comparability requires standard stimulus and task conditions. Since more complicated profiles (e.g., a characteristic pattern across different sensory modalities) of ERP components may be required to achieve desired specificity, standardization of these profiles will be essential to determine population rates.

**Reliability and stability in normal populations.** ERPs have been shown to be reliably measured. Stability is critical, as all other marker criteria depend on this property. Further studies of the stability of individual components and of profiles of components are needed in target-disorder populations, in comparison-disorder populations, and in normal control populations.

**Family aggregation and transmission in normal populations.** Given the assumption that an indicator is heritable, it is remarkable that the empirical evidence supporting this assumption is scanty. To our knowledge there are no well-designed studies evaluating transmission (inter-generation aggregation) of ERP parameters. Neither transmission of anomalous performance nor transmission of "normal" performance has been reported. Informative transmission studies require standardization for age effects because several generations are examined.

**Diagnostic specificity to the target disorder (schizophrenic and schizophrenic-spectrum disorders).** The sensitivity of individual ERP components is clearly not close to 1, suggesting pathophysiological heterogeneity of the target disorder (i.e., not all individuals with schizophrenic disorders exhibit ERP anomalies). The specificity of ERP components to schizophrenia is not close to 1, suggesting heterogeneity of the in-
dividual ERP vulnerability markers, such as P3b amplitude decrement (i.e., many individuals without schizophrenic disorders exhibit ERP anomalies). It is still possible that characteristic profiles of multiple marker indices may be derived that demonstrate diagnostic specificity. However, it is known that statistical verification of profiles requires large sample sizes, so collaborative investigation may be needed to achieve sufficient statistical power.

Conclusions and Directions for Future Research. Although some new studies have used the family-study approach, we are not very far along in the validation of ERP indices as markers for the liability to schizophrenia. The slow progress may be partly due to researchers’ reliance on the oddball paradigm, which, although it assesses cognitive function, may do so in too general a fashion to provide indices specific to schizophrenic pathology. In addition, the P3b component is most likely generated in widespread areas of the brain, depending on task, making it unlikely that the component will be selectively abnormal in a single population of disordered subjects (see also Vaughan 1978).

Paradigms are needed that directly assess the range of information-processing deficits seen in the schizophrenic syndrome in an attempt to link those deficits to hypothesized (and localizable) brain pathology. For example, one major hypothesis is that schizophrenia is caused by abnormal laterality in the medial temporal lobe (e.g., Crow 1990). This hypothesis leads to the testable expectation that schizophrenia subjects do poorly on some aspects of memory functioning. In fact, some preliminary evidence suggests that this is so (e.g., McKenna et al. 1990). There are currently proven methods for studying memory from an ERP vantage point, and a number of robust findings have been published (e.g., Friedman 1990). These paradigms could be applied to the psychophysiological study of schizophrenia.

Other experimental designs that could be exploited are selective attention and semantic priming. Both cognitive functions have been reported to be altered in schizophrenia (for ERP examples of selective attention and semantic priming, see Michie et al. 1990 and Koyama et al. 1991, respectively). These kinds of paradigms allow a finer grained analysis of cognitive processes than does the oddball paradigm.

Attempts must be made to use the full power of the endogenous ERP technique. The fact that the ERP has exquisite temporal resolution has led to success in associating given ERP components with stages of information processing (Hillyard and Picton 1987). However, the spatial information in the ERP has yet to be fully utilized. Scalp distribution has been largely neglected as a means of distinguishing patients and control subjects. More recent techniques that allow one to attempt to localize where in the brain ERP components are generated (e.g., Scherg 1990) may also prove fruitful in interpreting differences between patients and control subjects. The combination of these temporal and spatial sources of information, along with the study of other endogenous ERP components (e.g., mismatch negativity, processing negativity, N400, and slow wave) may provide more robust and valid putative biological markers (and marker profiles) than are currently available.

References


Garmezy, N. The psychology and psychopathology of attention.


Pfefferbaum, A.; Ford, J.M.; White, P.M.; and Roth, W.T. P3 in schizophrenia is affected by stimulus modality, response requirements, medication, and negative symptoms. Archives of General Psychiatry, 46:1035–1044, 1990.


Roth, W.T.; Pfefferbaum, A.; Kelly, A.F.; Berger, P.A.; and Kopell, B.S. Auditory event-related potentials in...


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