Electrophysiological and Behavioral Signs of Attentional Disturbance in Schizophrenics and Their Siblings

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The identification of individuals at increased risk for the development of schizophrenia requires intensive investigations of potential markers of vulnerability. Consanguinity has been one of the more accurate predictors of the development of schizophrenic disorder. Thus, one of the most important approaches has been the study of twins concordant or discordant for schizophrenia. However, twin findings indicate that there are both genetic and nongenetic components in the etiology of the disorder (1). Complementary strategies involve study of children of schizophrenics (2), including adopted-away offspring (3), and adult first-degree relatives of schizophrenics (4,5). The Pittsburgh project is an ongoing study in which a variety of neurobehavioral measures are being examined in probands and their adult siblings. The program focuses on the information-processing deviations associated with schizophrenia.

The concept of vulnerability to schizophrenia has been employed in order to examine the confluence of different etiological factors, both biological and psychosocial, that contribute to the onset of episodes (6). An examination of patients both during and following episodes can provide information on whether a marker is indicative of current psychopathology (state or episode marker) or of long-term vulnerability (trait) characteristics, present even between episodes (7). Ideally this would include pre-episode status, but such data cannot be collected except in the case of high-risk studies of children or adolescents. However, the presence of the marker among the siblings (or other first-degree relatives) of the patients could indicate either that the marker runs in families or that individuals at high risk who might eventually develop schizophrenia might also exhibit the marker.

More recently it has become clear that members of a proband's family are at greater risk not only for schizophrenia, but for related schizotypal personality disorders, all of which fall into the category of schizophrenia spectrum disorders (4,8,9). This led us to conceptualize the presence of markers among family members in a somewhat more specific manner. If the marker occurred only among those probands and siblings with schizophrenia spectrum disorder, then the marker was likely to be associated with the schizophrenia spectrum. If the marker also appeared at higher rates among those siblings who show nonspec-
trum disorders (e.g., affective disorder or other personality disorders), then it is a sign of general psychopathology not specific to the schizophrenia spectrum. However, if the marker is also found among siblings with no history of psychiatric problems, then it is most likely to be a true vulnerability marker that is associated with familial status but not specifically predictive of which family members will develop the disorder.

It was necessary to limit the scope of the present studies in several ways. Because many potential markers have been identified (10), it seemed critical to determine which of these to retain for future large-scale family studies. A wide variety of diagnostic, psychophysiological, behavioral, and neuropsychological measures has been included, but pragmatically at a cost of examining only limited numbers of patients and their relatives. The initial research approach has been to test only a single brother of each male proband, although later studies will be extended to female probands and multiple family members. In addition, an attempt is made to recruit randomly selected male siblings, so that the bias for recording only the most conveniently available or willing brother is minimized. In order to obtain a sample of patients who would be maximally functional, recruitment has been targeted at outpatient probands and their families, so that the proband would be capable of participating in most phases of the research. The present overview of attentional factors is based on data from an initial sample of 79 subjects.

OVERVIEW OF SUBJECT SELECTION AND EXPERIMENTAL MEASURES

The 30 schizophrenic probands (mean ± SD = 36.6 ± 6.9 years old), recruited primarily through the Veterans Administration Medical Center, were clinically stable, showing either no current exacerbation of psychotic symptoms, or no change in general clinical state for two monthly interviews prior to laboratory testing. All met RDC and DSM-III criteria for schizophrenia or schizoaffective disorder, mainly schizophrenic type. Of their 30 brothers (37.0 ± 9.2 years old), the participation of the first randomly selected sibling was obtained in 23 cases. Control subjects, recruited through advertising, consisted of 19 males (34.4 ± 7.9 years old) who met criteria for having no history of psychopathology and whose mean socioeconomic and educational levels were matched to the siblings. In addition, exclusion criteria for all subjects included possible brain damage or major medical problems, and siblings were excluded from the present analysis if they met criteria for schizophrenia.

The diagnostic battery for all subjects included the Schedule for Affective Disorders and Schizophrenia (SADS), Lifetime version (11; or SADS—Current version for patient follow-ups), Family History RDC, and drug-use and health questionnaires. Siblings and controls were also administered the Structured Interview for DSM-III Personality Disorders (SIDP; refs 12,13), and the Schedule for Schizotypal Personalities (SSP), which is a section of the Schedule for Interviewing Borderlines (SIB; ref 14). The latter two instruments were employed for evaluation of Axis II personality-related disorders. Psychiatric diagnoses were determined for all subjects following initial clinical evaluations and diagnostic evaluation conferences in which clinical staff and the project psychologist and psychiatrist participated. Diagnoses of schizophrenia spectrum disorder were assigned to four of the siblings (only one of whom had a prior history of alcohol abuse), and diagnoses of non–schizophrenia spectrum disorder (primarily affective disorder or previous alcohol-related problems) were assigned to 15 of the siblings. Siblings with current substance abuse or dependence problems were excluded. Unfortunately, it has been our experience that alcohol-related problems occur at a high rate among the siblings of
these patients, making a study of siblings with no history of alcohol-related problems impractical. No psychiatric disorder was diagnosed in the remaining 11 siblings.

The primary psychophysiological evaluation involved the recording of event-related brain potentials (ERPs), pupillary dilation, and heart rate in response to auditory stimulus processing during Counting and Choice Reaction tasks. In addition, smooth-pursuit eye movements, pupillary light reactions, and blink rates were recorded.

Behavioral evaluation included the Continuous Performance Test (CPT) using degraded visual stimuli, the Span of Apprehension task (SOA), and shadowing of dichotically presented material. In collaboration with John Watson and Michael Pogue-Geile, we initiated a neuropsychological test battery that included the Wisconsin Card Sorting Test (WCST), Trails B, the Relational Concepts subscale of the Luria-Nebraska Battery, and subtests of the WAIS-R (Information and Block Design) to assess general intelligence.

EXTRACTING FACTORS OF ATTENTIONAL PERFORMANCE

For an initial examination of data we were faced with the difficult task of trying to discriminate meaningful patterns within this extensive data set. Our attention was therefore drawn to an analysis of neuropsychological data performed by Mirsky (15) in which factor analysis of data from a broad background of neuropsychiatric patients had indicated the following four primary factors attributed to aspects of attentional processing:

Factor 1 (Focus/Execute: perceptual/motor speed) loaded on scores derived from the Trail Making, Talland Letter Cancellation, Digit Symbol Substitution, and Stroop tests.

Factor 2 (Sustain: vigilance) loaded on errors of omission and commission, and reaction time from the CPT.

Factor 3 (Encode: numerical mnemonic) was related to performance on the Digit Span and Arithmetic subtests of the WAIS-R.

Factor 4 (Shift: flexibility) was most heavily loaded on WCST errors.

These results were especially intriguing because of their relation to varieties of attentional disturbance that, as Mirsky noted, had been suggested a decade earlier by Zubin in an analysis of schizophrenic performance (16). Since there was some overlap between the variables included by Mirsky and those in our ongoing research, it seemed feasible to model a similar analysis using a subset of data. The neuropsychological data were limited to the Trails B, Relational Concepts, Block Design scores, and both perseverative and nonperseverative errors on the WCST. Behavioral tests included measures of sensitivity (d') and response criterion (Beta) from the CPT, and performance on the SOA in the nine-distractor condition (in which one of two different target letters is presented tachistoscopically with nine other nontargets).

For psychophysiological evaluation, the amplitude and latency of the P300 component of the ERP (17,18) were measured at multiple scalp sites during basic information-processing tasks. Decreased P300 amplitude among schizophrenics is one of the most reliably documented phenomena (19, 20). Two different auditory stimuli, with different overall frequencies of occurrence, were presented during two separate tasks. In the Counting task, the infrequent tone was counted by the subject. In the Choice Reaction task, separate motor responses were made to infrequent and frequent tones. The infrequent tone gave rise to the largest P300 component. The amplitude and latency of P300 to infrequent tones, measured over the midline parietal cortex, were entered into the analysis.

The loadings of each variable on four fac-
FIG. 1. Elements of attention extracted from the family study. Shown are loadings for individual items on the first four orthogonal factors derived from the factor analysis across all subjects. Key: RelC, Relational Concepts; Blk, Block Design; TrB, Trails B; WiN, Wisconsin Card Sort/Non-Perseverative Errors; WiP, Wisconsin Card Sort/Perseverative Errors; P3ac, P300 amplitude, Counting task; P3ar, P300 amplitude, Choice Reaction task; P3lc, P300 latency, Counting task; P3lr, P300 latency, Choice Reaction task; d', CPT, visual sensitivity; Beta, CPT, response criterion; Span, number correct, Span of Apprehension.

tors resulting from this analysis (totaling 63.9% of the variance) are schematically depicted in Fig. 1. Factor 1, comprised of neuropsychological test measures, appears related to Mirsky’s first factor (Focus/Execute) but also includes WCST errors. Factor 4, composed of CPT and SOA scores, is similar to Mirsky’s second factor (Sustain). Factor 2 includes the amplitudes of the P300 component on both tasks, while Factor 3 is separately loaded on P300 latency for both tasks. These physiological factors appeared to assess a type of processing independent from that seen with the neuropsychological and behavioral assessments.

Guided by the outcome of the factor analysis, the individual factors were examined. Since the emergence of factors was based on variance of the combined groups and did not necessarily indicate differences among groups of interest, it became important to focus on items composing each of the factors. Differences in neuropsychological performance, most marked for the patients, were also seen for siblings, especially those with spectrum disorders, on the Relational Concepts subtest of the Luria-Nebraska battery, for perseverative errors on the WCST, and on Trails B. (Further description of the neuropsychological data appears elsewhere; see refs. 21,22.)

BEHAVIORAL AND ELECTROPHYSIOLOGICAL COMPARISONS

The remainder of this discussion deals with the vigilance and psychophysiological variables. Comparisons were made among
controls, probands, and siblings of the probands meeting criteria for schizotypal personality disorder, other (nonspectrum) psychiatric disorder, and no diagnosis. Because the number of siblings to date who met criteria for schizotypal personality disorder is small, the initial analyses are considered exploratory. Missing data for any subject are indicated by reduced sample size.

The factor associated with sustained attention was related to performance on the CPT and the SOA. Visual sensitivity, as measured by $d'$ level, and response criterion (Beta) are illustrated for all groups in Fig. 2. One-way ANOVAs among all groups yielded a significant effect only for $d'$ ($F(4,73) = 4.29, p = .0036$). Probands and the spectrum-disordered siblings showed similar performance levels, and both scored significantly lower than controls. Those siblings with no diagnosis had the highest $d'$ scores. Their performance, like that of the controls, was similar to Nuechterlein's results for controls on a comparable version of the CPT ($d' = 2.56$; refs. 23 and Nuechterlein, personal communication). The diagnostic groups did not differ significantly on Beta. The $d'$ level findings are especially interesting given a lack of differences in Beta, which measures willingness to respond. This finding held even after the elimination of data for two probands with extremely high Beta values. The differences in visual sensitivity are therefore more likely to reflect basic differences in sensitivity not attributable to the subjects' criteria for responding.

No significant differences were found for the number of correct responses on the SOA. Numerically, probands and siblings with non–schizophrenia spectrum disorders exhibited a lower mean correct score (30.5 and 30.7, respectively, for a maximum of 40 trials) than did siblings with spectrum disorder, siblings with no diagnosis, and controls (with means of 32.5, 32.2, and 32.5, respectively).

Several unusual trends appeared in the analyses of the P300 component of the ERP to the rare stimulus (Fig. 3). None of the ANOVAs of the five groups was significant, though a trend for differences was observed for P300 amplitude in the Counting task ($p < .085$). In both tasks, smaller mean amplitudes can be seen for both probands and for those siblings meeting criteria for schizophrenia spectrum disorder as compared with all other groups. Furthermore, a prolongation of latency is seen in both tasks only for the spectrum-disordered siblings, even when compared with probands.

The lack of a strong P300 amplitude difference between controls and schizophrenic probands is atypical for most studies. (Analyses of all experimental conditions, including both infrequent and frequent stimuli at six electrode sites, did show significant differences between patients and controls for the Counting task, but did not reach significance for the Choice Reaction task.) The relatively stable functional level of our patients, who had remained out of the hospital for a mean of 39.2 months prior to testing, may be related to these effects. These results suggest that P300 amplitude may not reach normal-equivalent levels in remitted patients. This is not necessarily contradictory to previous findings showing that changes in P300 are associated with clinical improvement (24-27). Thus, P300 amplitude findings seem to fit criteria for a "mediating vulnerability factor" (28), a description applied to indicators that may vary with fluctuations in symptomatology but that even during asymptomatic periods never attain normal levels.

The present ERP results for siblings are also difficult to reconcile with the study of Saitoh et al (29), who reported highly reduced P300 amplitudes (based on an amplitude averaged over several time points) recorded from relatives of schizophrenics during a linguistic auditory discrimination task. A possible confound in the Saitoh et
FIG. 2. Mean values (± SEM) for d’ and Beta recorded in the Continuous Performance test. From left to right, data are presented for schizophrenic probands (Schiz), siblings with a diagnosis of spectrum disorder (Spect), siblings with other psychiatric disorders (NonSp), siblings with no disorder (Unaff), and controls.
FIG. 3. Mean (± SEM) values for P300 amplitude (top) and latency (bottom) to the infrequent auditory stimulus in the .33 condition at the midline parietal scalp location for all subject groups, as in Fig 2. Data are presented for the Counting task (left) and for the Choice Reaction task (right).
al study is that one half of the relatives of patients who participated were not related to patients also included in their study; however, this alone would probably not account for the discrepancy with the current data.

Among the siblings, only those with schizotypal personality disorder showed trends for both decreased P300 amplitudes and for increased latency. Increased P300 latency in schizophrenics has been reported in other patient samples (20). Both effects are considered deviant characteristics of the ERP response. Whether the lack of statistical significance for spectrum-disordered siblings is due to the small size of this group so far, or is indicative of true measurement error, will require further testing of relatives.

The spectrum-disordered siblings also showed significant decrements in visual sensitivity, similar to those noted in the patients. Across these measures of attention and information processing, a pattern similar to that seen in patients is emerging. It should be noted that among the spectrum-disordered siblings, none had been treated for psychiatric disorder (one had been referred to a social worker for family problems). Thus, the findings are not related to functional impairment identified with psychopathology even among these relatives of patients. Furthermore, it suggests that more refined analyses of symptomatology should be examined. Siever and colleagues (30) have also reported an association between smooth-pursuit eye-movement impairments and schizotypal characteristics, which lends further support to the notion that there is a broad pattern of attentional impairment associated with schizophrenia spectrum disorders, including schizotypal personality disorder. To this end we are studying how the occurrence of symptoms of schizotypal personality disorder among the relatives of patients may relate to laboratory variables, regardless of whether the subject meets clinical criteria for the disorder.

**IMPLICATIONS FOR THE CONCEPT OF VULNERABILITY TO SCHIZOPHRENIA**

The presence of attentional dysfunctions associated with schizophrenia spectrum disorders provides important information for refining the model of vulnerability to schizophrenia. The schizophrenia spectrum includes both schizophrenic patients and individuals with schizotypal personality disorders of lesser severity. The major components of the vulnerability dimension (6,7) have been thought to reflect primarily genetic factors, enduring biological factors (e.g., viral infection or postnatal brain damage), and/or residual effects of other major life experiences.

It might be expected that those with spectrum disorders lie along a region of greater vulnerability, and that within the same families the schizophrenic patients have the greatest vulnerability. A modification of this notion, suggested by Mirsky and Duncan (31), is that the vulnerability dimension is related to schizophrenogenic brain abnormalities. They suggest that between the threshold for adaptive behavior and the occurrence of schizophrenic episodes is a region in which stress leads to schizotypy or other spectrum disorder.

An alternative possibility is that there is greater similarity in vulnerability among those family members who exhibit schizophrenia spectrum disorders, although they may differ in severity of symptoms. In this case, it is necessary to account for the differential ability of these individuals to cope with stressful life situations. One solution is provided by introducing the moderating effect of tolerance to stress into the vulnerability model (Fig. 4).

According to this depiction of the model, increasing tolerance for individuals with low vulnerability would have little observable effect, since they are least likely to exhibit spectrum disorders at all. For those with greater vulnerability, mechanisms for enhancing tolerance to stress would be more effective in reducing the likelihood of
expressed symptoms. Several mechanisms for increasing tolerance are well known, including interventions through pharmacotherapeutic and psychotherapeutic treatment. In effect, the model embodies one of the goals in employing such treatments—reducing symptoms by increasing the patient’s ability to cope with typical as well as unusual life events.

As depicted, this version of the model also suggests that, in cases involving extremely high degrees of vulnerability, it may be difficult to provide sufficiently powerful interventions for raising the threshold of tolerance. For such individuals, even with the best of the currently known interventions, the likelihood that they will continue to vacillate between stages of minimal and severe symptomatology will remain high.

In pursuing the goal of understanding the factors that contribute to vulnerability to schizophrenia and other schizophrenia spectrum disorders, we are encouraged by the convergent findings from behavioral and psychophysiological studies. Family studies and approaches designed to link

FIG. 4. A modified model of vulnerability to schizophrenia and the effects of tolerance to stress. Changes in the threshold for onset of symptoms are related to variations in individual tolerance to stress. (Adapted from ref. 7.)

laboratory and refined diagnostic tools will provide critical information in efforts to understand the nature of schizophrenia.

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