Biological Markers in Schizotypal Personality Disorder

by Larry J. Siever

Abstract

The establishment of the new diagnostic category, Schizotypal Personality Disorder (SPD), has stimulated biological studies of patients with this disorder. Such studies offer the potential of better understanding the diagnosis and treatment of SPD as well as more clearly defining the boundaries of the schizophrenic disorders. SPD has been studied in the clinical setting, in family studies of schizophrenia, and in the biological high-risk paradigm. In most cases, biological variables associated with schizophrenia have been evaluated. Decreased activities of plasma amine oxidase and platelet monoamine oxidase have been associated with SPD in the families of schizophrenics and in "biological high-risk" studies. Smooth pursuit eye movement (SPEM) impairment has also been associated with SPD in a "biological high-risk" study of college students. Inferior backward masking performance has been demonstrated in SPD patients in the clinical setting. Other studies using psychophysiological measures have been applied to subjects with psychological characteristics similar to DSM-III SPD and found biological abnormalities similar to those reported in schizophrenia. These studies are consistent with the possibility that some individuals with SPD may share common psychobiological abnormalities with schizophrenic individuals and may sharpen our understanding of SPD and its relationship to schizophrenia.

The investigation of biological markers in schizotypal personality disorder (SPD) is an attempt to characterize biologically a group of patients with a phenomenological and, in some cases, genetic relatedness to schizophrenia. Biological markers may serve as external validators by which to sharpen the boundaries of current DSM-III criteria for SPD (American Psychiatric Association 1980). Biological characterization of DSM-III SPD patients might also enhance the clinical treatment of schizotypal patients by contributing to (1) more informed differential diagnosis to distinguish SPD patients with overlapping clinical presentations but different underlying etiologies, (2) possible prediction of their relative responses to various treatment modalities, and (3) estimation of their clinical prognosis.

As research into biological markers of DSM-III SPD is in its infancy, the empirical part of this review is of necessity brief, but may point to future directions for research in this area. It is organized around those few biological markers that have been studied in this disorder.

Diagnostic Considerations

The conceptual basis for the diagnosis of SPD and the precise clinical characteristics generated by this conceptualization are crucial considerations in assessing biological markers for SPD. As reviewed by Kendler (this issue), a diagnosis of SPD based on a model of a genetic relatedness to schizophrenia (i.e., familial model) may be quite different from a diagnosis based on an inferred clinical similarity to schizophrenia. Criteria based on the familial model would be expected to characterize a group of patients with biological characteristics similar to schizophrenic patients despite

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phenomenological differences, while the clinical model would likely select patients with etiological biological determinants that might or might not be related to those observed in chronic schizophrenia.

The clinical model is based on observations made in the late 1940s and 1950s of patients in analytic therapy who revealed "primary process" symptomatology often observed in schizophrenic patients (Siever 1981). At that time, psychosis was considered to be more indicative of schizophrenia than affective disorder. Thus, psychotic-like symptoms such as magical thinking or transient psychotic phenomena were considered, particularly by dynamically oriented psychiatrists, to be indicators of a relatedness to schizophrenia (Hoch and Polatin 1949). Since the advent of lithium therapy, it has become increasingly clear that psychotic symptoms are often observed in patients with major affective disorders, particularly manic-depressive psychosis (Pope and Lipinski 1978). Thus, what was considered a clinical relationship to schizophrenia at that time may in fact have reflected etiological factors more related to the affective disorders or to less specific psychotic processes. It is of interest that many of these psychotic-like characteristics are included in diagnostic formulations of borderline personality (Gunderson and Singer 1975) and these formulations select patients who are more likely to have an increased prevalence of affective disorders and other severe personality disorders than of schizophrenia in their relatives (Stone 1977; Akiskal 1981; Loranger, Oldham, and Tulis 1982; Pope et al. 1983; Soloff and Millward 1983).

From the vantage point of a biological evaluation of SPD patients, the use of a model of SPD based on a familial relatedness to schizophrenia, which corresponds to the genetic model, would thus have the advantage of selecting patients who might be more biologically homogeneous and share biological markers in common with schizophrenia. Such a model could be of great value in understanding not only biogenetic factors in SPD, but also those factors that contribute to the genetic susceptibility to schizophrenia, without the confounding factors that reflect the pathophysiological consequences of having the acute illness (as in the example of hypertension given by Kendler, this issue). Patients selected on the basis of the clinical model, which emphasizes transient positive (psychotic-like) symptoms over negative (deficit) symptoms, might conceivably show biological abnormalities related to schizophrenia, but on the basis of the above considerations, the clinical model also might select some patients with biological factors related to the affective disorders or to a less specific vulnerability to psychotic-like decompensation.

As Kendler (this issue) delineates, the DSM-III criteria for SPD include criteria derived from both the familial and clinical traditions. To the extent that criteria derived from these two different models may select phenomenologically different patient groups, one might expect that patients selected on the basis of the mixed familial/clinical DSM-III criteria might select individuals with biological markers related to some instances to schizophrenia, but in other cases, to other forms of more general psychopathology. As studies vary in their methodological approaches and in the specific diagnostic criteria used, these issues are referred to explicitly in discussion of each of the biological factors studied in SPD.

Methodological Considerations

Biological markers in SPD can be examined using a variety of methodological designs, depending on the specific hypotheses of the investigators and the model of SPD on which they are based. One strategy, hereafter referred to as "genetic," is to evaluate relatives of schizophrenic patients clinically and biologically for abnormal markers characteristic of schizophrenia. An association between such a biological marker and schizotypal characteristics in these relatives might suggest a relationship to an underlying genetic vulnerability to schizophrenia. This approach has the advantage of selecting subjects who partially share a common genetic pool with chronic schizophrenic patients and thus may be a valuable source of information regarding the pathogenesis of both SPD and schizophrenia. It does, however, have the disadvantage of being a methodologically difficult and time-consuming strategy that has an undetermined relevance to the understanding of patients with schizotypal characteristics who are found in the clinical setting.

Another approach is the "biological high-risk" strategy in which individuals are selected from a volunteer population on the basis of the presence of the abnormal biological marker and then evaluated clinically (Buchsbaum, Coursey, and Murphy 1976). Thus, a biologically homogeneous population is selected without any prior knowledge of its clinical characteristics. The prevalence of SPD, as well as that of other psychiatric disorders, may be evaluated in subjects selected by a particular marker and comparable controls by clinical investigators unaware of the subject's biological status. A specific association between
a marker and SPD, if sufficiently robust, may be detected with this design. This strategy, like the previous one, has the advantage of avoiding confounding effects of acute illness, hospitalization, or other psychiatric treatments. In contrast to the previous strategy, this approach can demonstrate an association between a marker and a specific clinical picture in a more general population. Such an association cannot be interpreted, however, as evidence that subjects selected by virtue of schizotypal characteristics rather than by the marker would necessarily manifest the particular marker in question. Thus, this strategy also cannot necessarily identify biological factors associated with SPD as it may be observed in a clinical population, since there may be multiple etiological determinants of SPD. Furthermore, no definitive conclusions can be drawn as to whether the presence of the biological marker in question is a function of a genetic relationship to schizophrenia, although inferences may be made if the marker is genetically determined and characteristic of schizophrenic patients.

A third approach, called "clinical," is to examine patients with schizotypal characteristics and study them biologically. This approach has the advantage of examining patients who are found in the clinical setting. It has the disadvantage of potentially selecting a biologically heterogeneous group of patients, with the selection process depending on the precise clinical criteria used. For example, if schizotypal patients were selected on the basis of the clinical rather than genetic model, i.e., positive symptoms of transient hallucinations or referential thinking, biological factors might be heterogeneous and in some instances conceivably unrelated to schizophrenia. This strategy may be useful in defining the boundaries of schizophrenia, as well as in providing external validators of a given diagnostic system such as DSM-III and permitting refinement of criteria and/or designation of biologically different subgroups of SPD. A modification of this design as used by Chapman and others (Chapman, Edell, and Chapman 1980) selects subjects from a volunteer population on the basis of schizotypal psychopathology and evaluates such subjects. Such a strategy permits more selective psychopathological characterization, but may be less applicable to the clinical setting. Ultimately, a combination of these strategies might reveal relatively biogenetically and clinically homogeneous patient populations that could be designated as having SPD and exclude clinically related but distinguishable patients with different biological underpinnings.

Platelet Monoamine and Plasma Amine Oxidase

Decreased plasma amine oxidase and platelet monoamine oxidase (MAO) have been proposed as possible biological markers for both schizophrenia and SPD. The status of low platelet MAO activity in schizophrenia has been extensively reviewed elsewhere (Wyatt, Potkin, and Murphy 1979). Although reduced platelet MAO activity has been reported in schizophrenic subjects, it may have been due to the confounding effects of prior neuroleptic treatment and has also been observed in bipolar affective patients (DeLisi et al. 1982; Siever and Coursey 1985). However, evidence that low platelet MAO activity may be associated with genetic loading for schizophrenia has led to the hypothesis of a possible genetic relationship between low platelet MAO activity and a predisposition to some forms of schizophrenia (Baron and Levitt 1980).

Baron and colleagues tested this hypothesis in two studies. In the first, they used the genetic strategy, measuring both platelet MAO and plasma amine oxidase activity in the relatives of schizophrenic patients. They found that both were reduced and that those relatives who presented with symptoms of "borderline schizophrenia" as defined by Kety et al. (1975) had lower platelet MAO or plasma amine oxidase activity than the well relatives (Baron et al. 1983, in press). However, the overlap in MAO activity between affected (schizophrenic or SPD) and unaffected individuals was great enough that the investigators felt that platelet MAO's usefulness as a risk factor for schizophrenia was limited (Baron, personal communication).

The same investigators used the biological high-risk strategy by selecting individuals on the basis of the biological marker, low platelet MAO, and examining their clinical characteristics, with special emphasis on assessing schizotypal psychopathology (Baron, Levitt, and Perlman 1980). The subjects were 115 randomly selected college students and hospital employees who provided a blood sample for MAO activity and were assessed by the Schedule for Affective Disorders and Schizophrenia (SADS) and the Schedule for Interviewing Borderlines (SIB) (Baron and Gruen 1980), a structured interview schedule that assesses schizotypal and borderline characteristics. In addition, subjects were queried as to family history of psychiatric disorders using the Family History Research Diagnostic Criteria (FHRDC) and an abbreviated version of the SIB. Subjects were divided into
Smooth Pursuit Eye Movement Impairment

Dysfunction of the smooth pursuit eye movement (SPEM) system has been consistently reported in 50–85 percent of chronic schizophrenic patients (Lipton et al. 1983; Holzman et al. 1984). Recordings of the eye movements of schizophrenic patients reveal small saccadic intrusions and lagging of the eyes in their pursuit of a smoothly moving target such as a pendulum (Lipton et al. 1983). In contrast to low platelet MAO, this finding is not confounded by the contribution of neuroleptic medications (Lipton et al. 1983). Furthermore, it seems to have a substantial genetic basis (Holzman et al. 1974; Holzman, Levy, and Proctor 1976; Holzman et al. 1980). However, as is the case for platelet MAO, questions of specificity exist for SPEM impairment. Some studies suggest that 30 to 50 percent of manic-affective disorder patients also have abnormal eye tracking (Lipton et al. 1983). However, remitted schizophrenic patients show impaired pursuit not accounted for by medication while the inaccurate tracking that is observed in remitted bipolar patients seems to be more associated with their dosage of lithium (Iacono, Tuason, and Johnson 1981; Iacono et al. 1982). The pattern of tracking dysfunction also differs between the schizophrenic and manic-depressive patients (Iacono et al. 1982). Finally, a significantly greater proportion of parents of schizophrenic patients show impaired pursuit than do parents of manic-depressive patients, who do not differ in the prevalence of SPEM from parents of normals (Holzman et al. 1984). Thus, as SPEM dysfunction appears to be more of a genetic trait marker for schizophrenia than for affective disorder, it is a logical biological marker to investigate in relation to SPD.

Tracking accuracy has not been reported in relation to schizotypal psychopathology in the relatives of schizophrenic patients. A preliminary study using the genetic strategy, however, suggested the possibility that thought disorder was associated with impaired tracking in the relatives of schizophrenic patients (Holzman 1975).

The biological high-risk approach has been applied to SPEM dysfunction. This strategy was used to test the hypothesis that low accuracy or abnormal SPEM would identify individuals with schizotypal characteristics in a functional volunteer population. Two-hundred and eighty-four college students were screened for their tracking accuracy electrooculographically. Their records were rated qualitatively and quantitatively by blind raters. Those with the most accurate and those with the least accurate tracking were restudied in the laboratory by both electrooculographic and infrared tracking recorders. They also participated in an extensive series of clinical interviews and ratings including the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer, Endicott, and Robins 1978) as well as checklists of symptoms of DSM-III SPD, BPD, and other personality disorders using an extensive semistructured interview. They participated in psychophysiological tests that have been found to be abnormal in schizophrenia such as reaction time, galvanic skin response, average evoked potential (auditory and visual), and the continuous performance test. A blood sample was drawn for the assessment of platelet MAO activity. Subjects were examined neurologically with an examination procedure sensitive to soft neurological signs. Finally, subjects were tested with a battery of psychological tests including the Korschach, Minnesota Multiphasic Personality Inventory (MMPI),

a low-MAO group and a high-MAO group (based on platelet MAO activity two standard deviations below and above the mean, respectively). The low-MAO group was significantly more likely to show psychopathology on the SADS and the SIB, particularly on the DSM-III criteria for SPD. The relatives of the low-MAO probands were also more likely to show DSM-III SPD psychopathology than were the relatives of the high-MAO group.

These results are somewhat at variance with two other studies in which low platelet MAO activity was found to be associated with affective symptomatology (Coursey, Buchsbaum, and Murphy 1979; Haier et al. 1980) and a family history of suicide (Buchsbaum, Coursey, and Murphy 1976). In neither of these high-risk studies was an association reported between schizophrenia-like clinical features or psychological test data and low-platelet MAO activity.

It is possible that the modest association between SPD and low MAO in the relatives of schizophrenic patients may not be specific for schizophrenia-related psychopathology. Rather, low-platelet MAO activity seems to identify subjects broadly characterized by a certain lability of affect or arousal and stimulus-seeking as may be observed in paranoid schizophrenics, affective disorders, alcoholics, and "sensation-seeking" nonpatient volunteers (Coursey, Buchsbaum, and Murphy 1979; Haier et al. 1980; Siever and Coursey 1985). Low MAO thus may not be a specific marker for SPD but might identify individuals with a variety of more severe personality disorders.
Chapman Anhedonia Scale, and tests selected for their sensitivity in detecting thought disorder (Siever et al. 1982a, 1982b).

The low-accuracy trackers exhibited a significantly higher prevalence of DSM-III SPD and a higher prevalence of schizotypal characteristics than the high-accuracy trackers (Siever et al. 1984). The only schizophrenic (in remission) was found in the low-accuracy group. The difference between groups reached a higher level of significance when only those subjects who were confirmed as having low-accuracy tracking in the laboratory were compared to their high-accuracy counterparts. A significantly increased prevalence of subjects with a history of bipolar I or II disorders was found in the originally selected low-accuracy tracking group, but was not present in the confirmed low-accuracy tracking group. These subjects thus appeared less stably impaired in their tracking performance across trials. Other psychopathology, including history of major affective disorder or presence of DSM-III BPD, did not distinguish the low- and high-accuracy trackers. The most consistent clinical characteristics observed in the low-accuracy trackers were those related to a lack of social relatedness, i.e., less heterosexual satisfaction, fewer heterosexual contacts, fewer close friends and acquaintances, and poor rapport. Perceptual aberrations characterized only a subgroup of the poor trackers.

The psychological test performance also indicated that low-accuracy trackers were more socially withdrawn, socially anhedonic, and inhibited. They also performed more poorly on attention-control measures such as the Wechsler Adult Intelligence Scale (WAIS) Digit Span and Stroop Color-Word Interference Test and on perceptual-motor tasks such as the WAIS Picture Completion and Block Design, the Embedded Figures Test, the Chapman Perceptual Aberrations Test, and the Bender-Gestalt Test. In contrast, there were only weak or nonsignificant associations between eye-tracking deviation and measures of divergent thinking such as the Mednick Remote Associates Test and the Kent-Rosanoff World Association Test (Coursey, Siever, and Lees 1985).

Psychophysiological variables related to galvanic skin resistance and reaction time were significantly associated with low-accuracy tracking—particularly the set index, a reaction-time measure elevated in schizophrenia. Abnormally long latencies of visual evoked potentials were observed significantly more often in the low-accuracy tracking group (Siever et al. 1982a).

The low-accuracy trackers manifested more soft neurological signs, as may be observed in schizophrenic patients, than the high-accuracy controls. Although these signs did not, in most cases, reflect specific neurological impairment, they suggested a more subtle neurointegrative dysfunction in the low-accuracy trackers (Siever et al. 1982a).

Thus, low-accuracy or impaired tracking identified individuals with schizotypal characteristics and other biological findings that are observed in schizophrenic patients. These findings suggest that SPEM dysfunction may be an indicator of a genetic vulnerability to both SPD and schizophrenia. In contrast, impaired SPEM did not seem to be associated with other psychiatric disorders, except for the bipolar affective disorders where the impairment was not so consistent. The impaired SPEM seems to involve a more pervasive neurointegrative dysfunction that may relate to social withdrawal or detachment. One might speculate whether such a dysfunction, manifest as a defect in cognitive centering or focus (Holzman, Levy, and Proctor 1976), could have impaired the development of mutually gratifying attachments to others. The development of attachments seems to depend on well-modulated synchronous interactions that may be problematic for these poor trackers, who are apparently characterized by a relative incapacity to recruit required neuronal systems appropriate for such complex inter- actional behavior.

The characteristics identified in this study are much closer to those observed in the relatives of schizophrenic patients than those defined by the clinical tradition as related to schizophrenia. These observations, based on the study of a biological marker related to schizophrenia, lend weight to genetic studies suggesting that negative symptoms such as social withdrawal and poor rapport best characterize a group of patients biologically related to schizophrenia (Gunderson, Siever, and Spaulding 1983; Siever and Gunderson 1983).

It remains to be determined how schizotypal subjects identified in genetic or biological high-risk studies are related to patients in the clinical setting who present with schizotypal characteristics. Would these stably withdrawn individuals appear for psychiatric treatment? Psychiatric contacts may not be frequent in the schizotypal relatives of chronic schizophrenic patients (Gunderson, Siever, and Spaulding 1983). A study in progress (Siever, L.J., Klar, H., and Davis, K.L., unpublished data) at the Bronx Veterans Administration Medical Center of patients with a primary personality disorder (PD) diagnosis in an inpatient setting suggests, however, that over half of
these patients meet DSM-III criteria for SPD by the Schedule for Interviewing DSM-III Personality Disorders (SIDP) (Stangl et al. 1985). Disordered SPEM (discussed previously) and elevated ventricular-brain ratio (VBR) as measured by computed tomography, both putative biological markers for schizophrenia, were observed in some SPD patients. These findings raise the possibility that SPD patients may demonstrate biological abnormalities also observed in schizophrenic patients.

Approximately half of the SPD patients also met DSM-III criteria for borderline personality disorder (BPD). Patients in the DSM-III SPD-BPD group merited an SPD diagnosis largely on the basis of the psychotic-like symptom criteria of SPD, but otherwise were clinically similar to non-SPD BPD patients in their impulsivity and affective instability. In contrast, the SPD patients without a concurrent BPD diagnosis were more likely to satisfy DSM-III criteria for compulsive personality disorder, characterized by a consistently aloof, rigid adaptation and uniformly were characterized as having poor rapport with others (Siever et al. 1984). It is possible, then, that the BPD-SPD patients may be closer to BPD than SPD over a spectrum of clinical characteristics and meet SPD criteria only because of the DSM-III criteria derived from the clinical tradition (e.g., magical thinking or perceptual distortions) that may not be specifically related to schizophrenia. The non-BPD SPD patients cannot at this point be distinguished from the BPD-SPD patients on the basis of disordered SPEM and VBR. However, biological marker strategies may be useful in defining more clinically homogeneous populations who might eventually be targeted for specific treatment interventions.

**Backward-Masking Performance**

Backward-masking performance is a reflection of the speed of information processing and is found to be consistently impaired in schizophrenic patients. In this paradigm, a target stimulus is presented tachistoscopically and followed by a second stimulus, the masking stimulus, which is usually striking but not informational. The masking stimulus interferes with the test stimulus' reaching awareness, thus masking it. A greater exposure duration to the target stimulus is required for an 80 percent accurate recognition of target letters in schizophrenic patients compared to control subjects (Saccuzzo, Hirt, and Spencer 1974). Furthermore delusional schizophrenic patients need significantly longer time intervals between the target and masking stimulus, i.e., the inter-stimulus interval (ISI), for target recognition to take place (Saccuzzo and Miller 1977). These results suggest a deficit at a very early stage of visual information processing in schizophrenia. Although a genetic basis for backward-masking performance has not been determined, as in the case of SPEM dysfunction, the inferior backward-masking performance by schizophrenic patients may partially reflect underlying biological determinants and thus may qualify as a potential psychobiological marker for schizophrenia.

Sterenko and Woods (1978), using a modification of the Chapman "clinical" strategy, identified subjects from a college population with a 2-7-8 code type on the MMPI which selects subjects who show excessive dependency, impaired competence, anhedonia, and mild thought disorder considered to represent "schizotypes" as described by Meehl (1962). These characteristics resemble but do not exactly correspond to current DSM-III SPD. However, the 2-7-8 profile is seen in borderline patients as well (Kroll et al. 1981). Subjects with the 2-7-8 profile were compared with controls without abnormal MMPI subscale elevations and those with two elevated scales other than the schizophrenia scale. The 2-7-8 group showed a longer critical ISI (minimum interstimulus interval for recognition to take place) than did the controls without MMPI elevations. In the group with inflations of any two scales other than the schizophrenia scale, the score on the schizophrenia scale was a significant predictor of ISI. These results suggest that "schizotypes," i.e., individuals with some features in common with schizophrenic patients, may also have an impairment in their early information processing.

Braff (1981) used a clinical strategy, explicitly selecting a group of unmedicated schizotypal inpatients who met DSM-III criteria. He also used the backward-masking paradigm to compare the schizotypal subjects with matched groups of paranoid schizophrenic and depressed patients. Both the paranoid schizophrenic and schizotypal patients had significantly fewer correct detections of the target stimulus at a 300-ms ISI, and had increased vulnerability to masking stimuli at longer ISI's. These results corroborate earlier studies in suggesting altered early information processing in schizotypal patients.

In another example of the clinical selection strategy, Saccuzzo and Schubert (1981) also compared backward-masking performance in three groups of adolescents: schizophrenic patients, schizotypal personalities, and borderline personality adolescents with adjustment reactions. The schizotypal patients were diagnosed on the basis of the Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1978) for
schizotypal features. In contrast to the previous study, the schizotypal patients were not all medication free. The critical stimulus duration (the time required for identification of the target stimulus in the absence of the masking stimulus) did not differ between the schizotypal and adjustment disorder patients but was less in both groups than in the schizophrenic patients. When the target stimulus was followed by a backward-masking stimulus, the schizotypal patients made more errors than the adjustment disorder patients but fewer than the schizophrenic patients. These results were similarly interpreted as suggesting a deficiency in information processing. Since the critical stimulus duration was normal in the schizotypal patients, the investigators concluded that the deficit was not in the formation of an iconic image but, rather, a posticonic deficiency involving inefficient information transfer.

The biological high-risk strategy has not yet been applied in backward-masking studies. Although further exploration of this marker in SPD patients and its psychobiologic and genetic underpinnings is required, studies to date suggest a biological relatedness between DSM-III SPD and schizophrenia.

Other Biologic Markers in Schizotypal Subjects

Other biological markers have been examined less extensively in schizotypal subjects. Some of these studies stemmed from investigations of patients with borderline psychopathology. Biological markers, particularly those related to the affective disorders, have been explored in DSM-III BPD. As DSM-III BPD and DSM-III SPD frequently overlap, such markers have been examined in schizotypal patients as part of an examination of markers in borderline patients. One preliminary study of 15 dysphoric borderline inpatients used psychological test data (Carsky et al. 1981) to distinguish affective and schizotypal subgroups (Steiner et al. 1984). Two-thirds (six out of nine) of the affective subjects had an abnormal dexamethasone suppression test (DST), while only one of the six schizotypal subgroups had an abnormal DST (Steiner et al. 1984). This study raises the possibility that schizotypal patients may be discriminated biologically from more affectively disturbed patients in the borderline domain and are less likely to show biological abnormalities associated with the affective disorders.

Other psychophysiological tests have been examined in subjects, usually student volunteers, who have psychological characteristics considered to be related to schizophrenia in a modified clinical selection strategy. Although these subjects would not necessarily meet criteria for DSM-III SPD, they do demonstrate one or more characteristics on psychological testing that may be associated with a schizotypal personality. For example, Koh and Peterson (1974), using the clinical strategy, compared short-term memory functioning in a group of students showing the 2-7-8 code type on the MMPI and a control group without MMPI elevations. They presented the student with two displays of dots, one with more dots than the other, asking them to assess whether the second display contained more or fewer dots than the first. In group comparisons, the 2-7-8 group did more poorly than the controls. Another study (Koh, Kayton, and Schwarz 1973) found that similarly selected nonpsychotic schizophrenic patients were less efficient in unitizing overloaded verbal inputs at hierarchically higher code levels. These investigators interpreted both studies as representing a deficiency in processing verbal and visual inputs. However, the diagnostic specificity of the 2-7-8 profile is unclear as it is frequently found in borderline patients (Kroll et al. 1981).

Screening college students with the Chapman Physical Anhedonia and the Perceptual Aberration Scales has also provided a source of nonpsychotic subjects with a phenomenological resemblance to schizophrenia for psychobiological marker studies (Chapman, Edell, and Chapman 1980). Both scales were developed in an attempt to characterize psychosis-prone individuals. The Physical Anhedonia Scale emphasizes a relative inability to experience physical pleasure. The Perceptual Aberration Scale is designed to detect major distortions in bodily perceptions. Interestingly, deviancy in the two scales rarely coincides, with modest negative correlations being observed between scales in a large sample of college students. In one such study of college students, subjects with perceptual distortions showed more psychotic-like symptoms (e.g., brief illusions or referential ideation), as might be expected. However, they also had a significantly higher prevalence of prior affective disorders as diagnosed in the SADS than anhedonic or control subjects. The increased prevalence of hypomania in the perceptual distortion group was particularly striking in this regard (6 percent of control group, 8 percent of anhedonic group, and 22 percent of perceptual aberration group). These subjects were also more likely to have sought psychiatric treatment than the other two groups. In contrast, the anhedonic group was
more often socially withdrawn, with fewer dates and decreased sexual interest. For example, 22 percent of the anhedonics, compared to 5 percent of the perceptual aberrations and 3 percent of the control group, had neither gone steady in high school nor shown increased sexual interest since high school. Current criteria for DSM-III SPD would appear to identify individuals in both the perceptual aberration and anhedonia groups, although they perhaps more frequently identify the perceptual aberration group.

However, the perceptual aberration group may be more related to a proneness to affective disorder, while the anhedonic group shows more of the characteristics observed in the relatives of schizophrenic patients and individuals selected on the basis of SPEM dysfunction. Thus, the Chapman scales identify two distinct groups: a more stably socially withdrawn anhedonic group and a perceptual aberration group prone to affective disorder. These considerations must be taken into account in interpreting the following studies.

Reaction-time crossover is consistently observed in schizophrenic patients (Nuechterlein 1977) and represents an attentional impairment that may be related to a vulnerability to schizophrenia. Subjects defined as schizotypal on the basis of high scores on either the Perceptual Aberration Scale or the Physical Anhedonia Scale (i.e., clinically selected) were compared to controls on a reaction-time paradigm (Simons, MacMillian, and Ireland 1982). Both groups tended to show crossover, but this was more clearly the case for the perceptual aberration group. The low correlation between the two groups again suggests that they may represent distinct subtypes. Since reaction-time performance has not been extensively studied in affective disorders, it is difficult to determine whether the crossover in the perceptual aberration group is more related to affective disorders, schizophrenia, or a less specific vulnerability to decompensation.

Auditory event-related potentials were measured in a group of anhedonic college students identified by the Chapman Physical Anhedonia Scale and controls. The anhedonic subjects manifested a decreased late positive (P3) component when an auditory signal predicted a high-interest event, e.g., presentation of slices of nuclei fibers (Simons 1982). These results suggested limitations in higher-level arousal to sexual and related high-interest stimuli in the anhedonic subjects similar to results of studies of late components of evoked potentials in schizophrenic patients (Roth et al. 1984).

Electrodermal and cardiac orienting in response to auditory stimuli have also been studied in students identified by the Physical Anhedonia Scale and the Perceptual Aberration Scale (Simons 1981). Hyporaorous on these variables to auditory stimuli has been shown in some (Bernstein et al. 1981) but not all studies of schizophrenia (Zahn, Rosenthal, and Lawlor 1968). The anhedonic subjects showed the most consistent hyporesponsiveness in their orienting response, while perceptually aberrant subjects and normal controls exhibited normal orienting responses.

These studies raise the possibility that the anhedonic subjects, who are most marked by social withdrawal, manifest psychophysiological abnormalities observed in studies of schizophrenic patients while the perceptually aberrant subjects, who may have more affective psychopathology, are less consistent in showing biological abnormalities of the kinds noted in studies of schizophrenic patients.

Implications for Criteria of SPD

Although the studies of SPD and biological markers are few and, for the most part, preliminary, these results suggest that there are patients with schizophrenic-like characteristics who exhibit biological abnormalities similar to those observed in chronic schizophrenia and that these patients may represent a subgroup within the present DSM-III schizotypal domain. The presence of a biological marker or markers that define a group of schizotypal patients may be of great value in refining criteria for a personality disorder specifically biogenetically related to schizophrenia. Such a marker might provide an external validator for a clinical diagnosis of SPD and might also have predictive power for treatment considerations. A biological marker may also provide a bridge between genetic and clinical studies of SPD. Biological markers, particularly genetically determined ones such as SPEM impairment, may permit identification of individuals who share biogenetic determinants with schizophrenic patients even in the absence of a familial history of schizophrenia.

The criteria used to select schizotypal subjects in these biological marker studies have varied. However, in those studies in which individual schizotypal characteristics have been studied in relation to biological markers, characteristics such as social isolation, anhedonia, poor rapport, and suspiciousness—often observed in the relatives of schizophrenic patients—are more closely associated with abnormal markers (e.g., smooth pursuit impairment, hyporesponsive
orienting, and small evoked potentials) than are the perceptual aberrations emphasized by DSM-III. In fact, perceptual aberrations appear to select individuals prone to affective symptomatology, who are less likely to show biological abnormalities observed in schizophrenia. Thus, biological marker studies cumulatively converge with genetic studies (see Torgersen, this issue) in suggesting that characteristics such as marked social withdrawal, poor rapport, and decreased pleasure in social interactions may best define the schizotypal category. Individuals with these characteristics are similar to schizophrenic patients with regard to negative symptoms, but are not usually prone to psychosis and therefore rarely exhibit positive symptoms. These individuals may be discriminable from subjects with perceptual aberrations and affective instability. The latter group might best be excluded from the "schizotypal" domain and, in many cases, be considered as having BPD. They appear prone to decompensation but not necessarily to schizophrenia. A number of psychophysiological markers such as SPEM dysfunction, inferior backward-masking performance, and hyporesponsive orienting responses and evoked potentials could conceivably prove useful in discriminating stably "schizotypal" individuals, who resemble relatives of schizophrenic patients, from "psychotic-prone" individuals with positive perceptual and cognitive symptoms, who more often appear to be related to affective disorders or a more general vulnerability to psychosis or regression than to schizophrenia specifically. Subjects in the former group resemble schizophrenic patients in their capacity for psychosis. Biogenetic factors predisposing toward schizotypy and psychosis may both be required for schizophrenia to be present. Thus, for example, SPEM dysfunction and other psychophysiological abnormalities may reflect a core vulnerability in the control of perceptual-motor neural processes, which may become "amplified" to produce positive symptoms in schizophrenic individuals with a susceptibility to enhanced catecholaminergic, particularly dopaminergic activity (Siever et al. 1982a, 1982b).

Conclusions

The study of biological markers in SPD has been a relatively recent endeavor, but one that offers hope of improving diagnostic classification in the personality disorders as well as for understanding some of the biogenetic and environmental factors that may allow one individual to remain stably "schizotypal" and another to decompensate to schizophrenia. Markers associated with schizophrenia such as platelet monoamine or plasma amine oxidase, SPEM, backward-masking performance, and electrodermal orienting responses appear to identify some individuals with a resemblance to the affected relatives of schizophrenic patients and may be useful in sharpening our understanding of what constitutes "schizotypal personality disorder."

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