
by Steven O. Moldin and L. Erlenmeyer-Kimling

Abstract

The first aim of this issue of the Schizophrenia Bulletin is to provide an up-to-date review of the major domains of research in the experimental psychopathology of schizophrenia, in which important contributions to our understanding of putative pathophysiologic mechanisms have been made. This research has identified several biobehavioral traits as measures of enhanced liability to schizophrenia. Rather than present a substantive review of the research on a particular trait, the authors of several articles focus on a critical appraisal and evaluation of the literature since 1987 in their particular area. The second aim of this issue is to present new methodologic approaches and conceptualizations for incorporating biobehavioral trait data in future psychiatric research designs. Now is the time not only to recognize past contributions but also to recognize that further advances in our understanding of the etiology and pathophysiology of schizophrenia may depend on continued research in experimental psychopathology that culminates in an integration in both methods and research design across disparate scientific fields.


Psychiatric researchers have searched intensively for biobehavioral measures or characteristics that identify enhanced liability to schizophrenia and other mental disorders. Gottesman and Shields (1972) first applied John and Lewis' (1966) concept of "endophenotype" to schizophrenia to describe those external characteristics of the organism discernible to the eye only with aid. The term was originally used to denote biological attributes (e.g., enzyme activity, chromosomal morphology); given the recognition that the road from etiology to ultimate disease expression is long, the concept of endophenotype has been broadened in the study of mental disorders to categorize a wide range of biologic and psychologic processes that represent an intermediate state between causative mechanisms such as genes and overt symptomatic expression.

The potential benefits of identifying such attributes are manifold and include the following: (1) increased understanding and delineation of underlying pathophysiologic mechanisms with regard to biochemical and neuroanatomic alterations in normal biological functioning; (2) increased accuracy in identifying individuals who fall within a spectrum of illnesses related to a "core" disease phenotype; (3) increased accuracy in estimating recurrence risks to first-degree, second-degree, and more distant relatives of schizophrenia patients; (4) resolution of clinical heterogeneity; and (5) identification of biologically meaningful subtypes.

A great deal of empirical data dating back to the turn of the century has been gathered in the quest to establish endophenotypic traits as genetic, biochemical, or neuroanatomic signposts to the etiology of schizophrenia. The problem of untangling biological or

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biobehavioral deviance reflecting true liability from disturbances epiphenomenal to treatment, institutionalization, or the disease process itself requires a prospective research design in which individuals are studied before they become ill. Such a design would be impractical if subjects were drawn randomly from the general population, given schizophrenia's low lifetime cumulative incidence (0.85%–1%). Pearson and Kley (1957)—capitalizing on empirical risk figures available at that time, especially those drawn from the work of Kallmann (1938), that showed that schizophrenia was a familial disorder—proposed a prospective design in which offspring of two parents with schizophrenia, with their augmented risk of about 40 percent, could be studied intensively over time. Because of the difficulties of locating offspring of two parents with schizophrenia, however, most investigators subsequently opted for the more practical collection of samples of offspring with one affected parent, who had a morbidity risk of about 10 to 15 percent.

Several high-risk projects devoted in part to identifying biological or behavioral traits as indicators of liability to schizophrenia were initiated worldwide from the late 1950s through the early 1970s. While the full potential of these projects is yet to be realized, the first generation of high-risk research has produced encouraging findings that implicate a small number of biological and biobehavioral traits as measures of liability to schizophrenia (Erlenmeyer-Kimling 1987; Erlenmeyer-Kimling and Cornblatt 1987).

This issue has two main aims. The first is to provide an up-to-date review of several such biobehavioral traits as measures of enhanced liability to schizophrenia. Rather than present a substantive review of the research on a particular trait, the authors of articles with this purpose focus on a critical appraisal and evaluation of the literature in their particular area, with the primary emphasis on critical discussion of findings since 1987. The perspective on this research is not limited to that from high-risk or other genetic paradigms but includes discussion of relevant findings from other sources (e.g., diagnostic studies). The second aim is to present new methodologic approaches and conceptualizations for incorporating biobehavioral trait data in future psychiatric research designs.

To facilitate data evaluation and comparisons among several indicators, we asked the authors of the review articles to follow a general format that includes discussion of the following 12 points with respect to the indicator under review:

1. Is the measurement of the trait over time repeatable by different researchers, that is, is the measurement reliable?
2. Is the measure valid? While sufficient evidence to establish construct validity of a particular measure may be lacking, and given that schizophrenia is an open concept of indeterminate validity (Meehl 1990), is there evidence that the biobehavioral data can serve as “bootstraps” (Cronbach and Meehl 1955) on the way to more refined measurement of the disorder and improved understanding of etiology, pathophysiology, and phenomenology?
3. What is the range of indicator values (including age and gender effects when appropriate) in normal control or general population groups?
4. Is the indicator transmissible in normal families and does it co-segregate with schizophrenia in pedigrees with one or more affected members?
5. What is the mode of action of indicator deviance and hypothetical involvement in the pathophysiology of schizophrenia?
6. To what extent is the indicator associated with increased risk to schizophrenia—Do relatives or other individuals at increased risk for clinical disease have deviant indicator values?
7. Is standardized, objective, and quantitative measurement available?
8. What is the indicator’s specificity, sensitivity, and predictive power for detecting schizophrenia in clinical samples? High diagnostic efficiency would support the utility of the indicator as a laboratory measure (Robins and Guze 1970) of schizophrenia.
9. Is the indicator state-independent? Available followup data should be critically evaluated.
10. Is the indicator cost-effective—Is it practical to measure the indicator in research and clinical settings?
11. What are the specific problems and issues relevant to the particular indicator?
12. Are there any recommendations for future research?

Eight articles in this issue deal with specific domains of indicators. In the first, Cornblatt and Keilp (1994, this issue) review studies that have used various versions of the Continuous Performance Test to assess impairments of attention. A noteworthy aspect of their contribution is a discussion of preliminary data implicating subcortical brain dysfunction, particularly that...
associated with the basal ganglia and pathways connecting them to the frontal lobes, in attention deficits. Comblatt and Keilp also review studies implicating impaired attention in the personality development of individuals with a susceptibility to schizophrenia.

Levy and colleagues (1994, this issue) review the recent literature on eye tracking dysfunction, a bio-behavioral measure whose usefulness as an indicator of liability to schizophrenia is supported by a large body of empirical evidence. The authors offer recommendations to facilitate the comparability of eye tracking results across laboratories and discuss the role of both qualitative and global quantitative ratings of eye tracking dysfunction. Several of the provocative issues raised are discussed in greater detail in a longer article that appeared in an earlier issue of the Schizophrenia Bulletin (Levy et al. 1993).

The viability of cognitive event-related potential (ERP) indices as indicators of liability to schizophrenia is examined by Friedman and Squires-Wheeler (1994, this issue). Findings related to the P3, P50, and N100 components, mismatch negativity, and a longer latency ERP component (the slow wave) are reviewed. Methodologic issues that complicate this area of inquiry are analyzed at length, and a thoughtful discussion of the intracranial origin of ERP components and brain pathology in schizophrenia is provided. The authors discuss the need for investigators to pay greater attention to the scalp distribution of ERP components and profiles of multiple ERP indices.

Csernansky and Newcomer (1994, this issue) review the vast literature on biochemical markers and conclude that with respect to both dopaminergic and serotonergic systems there is little evidence that either basal cerebrospinal markers or plasma markers predict increased risk for the development of schizophrenia. Either their validity as correlates of brain monoamine function is uncertain or they are highly dependent on clinical state. The authors propose platelet and neuroendocrine markers of serotonergic function and an individual's capacity to decrease plasma homovanillic acid concentrations following antipsychotic drug blockade as less state-dependent measures of liability.

Structural brain abnormalities as measures of risk are reviewed in an article by Cannon and Marco (1994, this issue). The authors discuss evidence that measures of brain pathology (ventricular enlargement and limbic system pathology) are sensitive indicators of illness within families and that increases in brain pathology in schizophrenia patients and their relatives may be attributable to both genetic factors and environmental insults. The need for future studies to make longitudinal assessments and to employ more specific neuroanatomic measurements is discussed.

Neuropsychological risk measures are reviewed in the article, by Kremen and colleagues (1994, this issue). Although most such measures have not yet been adequately validated, the authors discuss several promising leads that have emerged from studies of the biological relatives of schizophrenia patients. Kremen et al. found the strongest evidence of impairment in relatives to be in sustained attention, perceptual-motor speed, and concept formation/abstraction; mental coding/encoding are implicated to a lesser extent. The pattern of deficits found in relatives paralleled that found in schizophrenia patients and suggested brain dysfunction in the prefrontal, temporal-limbic, and attentional systems. The authors discuss the importance of using appropriate psychiatric control groups, applying comprehensive test batteries, and integrating neuropsychological assessments with brain imaging techniques.

Lenzenweger (1994, this issue) discusses the effectiveness of psychometric measures (e.g., the Perceptual Aberration Scale) in identifying liability to schizophrenia or schizotypy in light of Mehl’s (1990) theoretical framework. The author discusses the sensibility of the psychometric high-risk paradigm in supplementing genetic studies to search for measures of illness liability. Important methodologic recommendations presented by Lenzenweger include the use of strictly objective measures and the inclusion of multiple psychometric indices that could be used with other promising bio-behavioral measures of liability. Lenzenweger emphasizes the importance of studying schizotypal subjects in the general population and outpatient samples to delineate indicators of liability to schizophrenia.

Miklowitz (1994, this issue) reviews the extensive literature in which family risk indicators with prognostic significance in schizophrenia—expressed emotion, affective style, and communication deviance—have been identified. Miklowitz discusses the utility of these variables as indicators of liability to illness and the contributions to these variables of biological and psychosocial factors. He presents a thought-provoking dis-
discussion of the sociopolitical under-
tones of family risk research,
which has important implications
for other areas of psychopathologi-
cal research on liability indicators
discussed in this issue.

Gruzelier and Raine have writ-
ten an article reviewing the value
of electrodermal measurement as
an indicator of liability to schizo-
phrenia and schizotypal personality
disorder. Because of space restric-
tions for this issue, their article
will be published in the Interna-
tional Journal of Psychophysiology.
In this provocative article,
Gruzelier and Raine (1994) review
data supporting delineation of fun-
damental syndromes in schizophre-
nia and schizotypy on the basis of
bilateral skin conductance record-
ing; two of the syndromes appar-
etly have some basis in im-
balance in hemispheric functions.

Three articles in this issue dis-
cuss ways in which biobehavioral
data can be incorporated in future
psychiatric research designs. Clar-
idge (1994, this issue) points out
that the search for a single “smok-
ing gun” measure of liability to
schizophrenia has not been suc-
cessful and has most likely been
hampered by heterogeneity and
difficulties in defining the clinical
disorder. Claridge discusses find-
ings from cognitive psychology,
psychophysiology, and the neuro-
psychology of hemisphere function
and argues that the clinical expres-
sion of vulnerability is attributable
to a convergence of several com-
ponents of risk that, individually,
are common in the healthy popu-
lation. Claridge discusses the dis-
tinction between subclinical defects
with variable expression and
biologically based personality
dimensions.

Moldin (1994, this issue) dis-
cusses the incorporation of bio-
behavioral trait data into such ge-
etic analytic techniques as path,
segregation, and linkage analysis.
Biobehavioral trait data can greatly
enhance the informativeness of
schizophrenic pedigrees and in-
crease the power for delineating
the mode of transmission of
schizophrenia and detecting link-
age of schizophrenia to deoxy-
ribonucleic acid (DNA) polymor-
phisms. In addition, Moldin
presents data supporting the use
of such information for refining re-
currence risk estimation and in-
creasing the power of linkage
analysis under genetically complex
models of inheritance. The article
presents a natural integration of
data and methods in the fields of
molecular genetics, genetic
epidemiology, population genetics,
and experimental psychopathology
for working toward an increased
understanding of the etiology of
schizophrenia.

In the last article, Rice and
Todorov (1994, this issue) present
an important approach for using
stability of diagnosis to model the
relationship between biobehavioral
data and the probability of being
a true case. This approach follows
previous work by Rice, in which a
model using followup data and
based on the standard epidemi-
ologic approach of using sensitivity,
specificity, and true base rate was
developed and applied to analyze
the stability of affective disorder
diagnoses (Rice et al. 1992). The
incorporation into suitable stability
studies of data from the areas of
research discussed in this issue
could facilitate the development of
a nosology of schizophrenia based
on both phenomenology and
presumed pathophysiologic
mechanisms.

Overall, this issue presents a re-
view of the major domains of re-
search in the experimental psycho-
pathology of schizophrenia. This
field has made important contribu-
tions to our understanding of
putative pathophysiologic mecha-
nisms, and the elucidation of bio-
logical mechanisms important in
the pathogenesis of the illness has
always been a clearly defined goal.
Further advances in our under-
standing of the etiology and
pathophysiology of schizophrenia
may depend on continued research
in experimental psychopathology
that culminates in an integration,
in both methods and research de-
sign, across disparate scientific
fields. Such an integration will al-
low us to identify highly sensitive
and specific multidimensional in-
dices of liability.

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