Schizophrenia Reviewed: Toward an Integrative Genetic Model

William G. Iacono and William M. Grove
University of Minnesota

At no time in the history of schizophrenia research have the expectations for new discoveries that might elucidate the causes of this baffling disorder been higher. Much of this hopefulness stems from recent advances in neuroscience and molecular biology that provide tools for exploring schizophrenia that were unimaginable two decades ago. The excitement generated by the opportunities these new procedures offer has begun to dominate current research. This was clearly evident at the 1993 meeting of the International Congress on Schizophrenia Research, at which over 70% of the nearly 400 poster presentations involved biological themes.

The promise of new technology notwithstanding, these two Feature Review books, which together give a comprehensive overview of schizophrenia research, provide a sobering reminder of just how elusive progress has been in this field. The past 100 years of investigation have contributed little to unravel the mysteries of this disorder. In a field in which replication failure is the rule rather than the exception, few correlates of the disorder are generally accepted as reproducible, and fewer still have potential as etiological clues.

SOME FACTS ABOUT SCHIZOPHRENIA

The most encouraging line of investigation comes from family, twin, and adoption studies. These reports have established beyond reasonable doubt that genes somehow contribute to the etiology of schizophrenia and related spectrum disorders. No specific environmental factor has been shown to be sufficient to cause schizophrenia. However, the high degree of discordance for schizophrenia among monozygotic twins (perhaps 50%) indicates unequivocally that there is a significant environmental contribution. How the environment interacts with genetic risk to trigger the development of schizophrenia remains unknown.

To determine how the genetic diathesis for schizophrenia is transmitted, psychopathologists have used quantitative and biological strategies such as segregation and linkage analysis. In segregation analysis, family data are used to evaluate models positing effects of single genes, polygenic aggregates, and combinations thereof. These models are now easily fit by computer programs that allow for sex-modified effects, reduced penetrance, variable age of onset, and the influence of other variables, such as environmental factors, on risk of illness. Models of schizophrenia that posit a single gene acting alone cannot account for observed family data. Polygenic and mixed models, the latter involving both major and polygenic, are accommodated equally well. The revolution in molecular biology makes it possible to use linkage analysis to determine if the presence of schizophrenia is correlated with chromosomally localized DNA within families. However, the numerous linkage studies conducted to date have failed to generate meaningful leads concerning the genetics of schizophrenia.

The evidence supporting these conclusions is summarized in both of the featured volumes, Gottesman's book, which updates his earlier thought-provoking review of the relevant behavioral genetic literature, provides an especially thorough treatment of this subject matter despite being written for a general audience. Comparing this current volume and his other books, however, reveals that recent research has provided few new insights into the genetics of schizophrenia. Data consistent with the findings noted above have been available for decades. Recent studies have merely reaffirmed earlier findings with sounder methodology and modern diagnostic criteria.

Streube and Oades's scholarly book, however, provides a more extensive treatment of the schizophrenia literature, including coverage of theories, neurophysiology, neuroanatomy, psychophysiology, information processing, and longitudinal high-risk investigations. Our interpretation of their review leads to the following broad conclusions about the state of the field.

Theory

There is no plausible, comprehensive theory of schizophrenia that can account for its many manifestations. What theories there are tend to deal only with certain aspects of the disorder (e.g., attention, specific symptoms), have small followings, have limited heuristic value, and be difficult to falsify. A prime example of a popular theory with some of these attributes is the vulnerability-stress theory, which states that constitutional predisposition and environmental stress combine to cause schizophrenia. As difficult as it is to argue against such a commonsense notion, it is also difficult to generate falsifiable hypotheses from it.

Neurophysiology

The neurochemistry of schizophrenia is too complex to be explained easily by activity in a single neurotransmitter system. The 30 years of intensive effort spent pursuing the dopamine hypothesis make it seem likely that dopamine is involved in schizophrenia in some way. However, there is still no incontestable demonstration that the biochemical basis of schizophrenia rests with disturbed dopaminergic functioning. For example, recently, Su et al. (1993) failed to find any evidence for genetic linkage between the

List of Books

dopamine D<sub>2</sub> receptor and schizophrenia.

**Neuroanatomy**

Although there has been no consistent demonstration of a brain lesion or dysfunction associated with schizophrenia, the large number of studies reporting a variety of brain anomalies can be taken to indicate that at least a subgroup of schizophrenics have some type of abnormality in the central nervous system. Static and functional imaging as well as neuropsychological studies point to the frontal lobes as a likely site.

**Psychophysiology**

Schizophrenic patients, especially those with chronic schizophrenia, have been shown repeatedly to be electrodermally nonresponsive to innocuous stimuli, have excess low-frequency electroencephalographic activity and diminished alpha (especially frontally), have reduced amplitudes of the late components (P300) of the event-related potential, have deficient sensory gating as indicated by a failure to suppress the second in a series of early brain potentials (P50) in an auditory conditioning paradigm, and have dysfunctional smooth-pursuit eye tracking. Other than these being familial resemblance for some of these measures in the relatives of people with schizophrenia, the significance of these observations remains unclear because they have few well-established correlates.

**Information Processing**

Although attentional disturbance has long been viewed as a core component of schizophrenia, no specific, clearly delineated attentional deficit is known to characterize schizophrenia. This area of research has generated some well-established experimental paradigms in which both schizophrenics and their relatives have been noted to perform abnormally. Chief among these paradigms are the continuous performance, span of apprehension, and reaction time crossover tasks.

**Longitudinal High-Risk Studies**

Investigations of the offspring of schizophrenic parents have yet to shed important insights into the development of this disorder, in part because the studied offspring are still passing through the age of risk and in part because some of the variables commonly examined in schizophrenic adults may not be age-appropriate for children. High-risk children have been found to perform poorly on span of apprehension and continuous performance tasks.

**Markers of Genetic Vulnerability**

A number of variables, because they have been shown to be deviant in both schizophrenic patients and their well relatives, have been considered as possible indicators of genetic liability for schizophrenia. The single best such measure is smooth-pursuit eye-tracking dysfunction, which has been associated with schizophrenia without exception in more than 40 reports worldwide and found in the relatives of schizophrenics in over 15 studies without failure of replication. Other promising variables with marker potential derive from the span of apprehension and continuous performance tasks, the reaction time crossover effect, and event-related potential paradigms involving P50 and P300 brain potentials.

Where do investigators go from here? Neither of the books under review tackles this question directly, nor does either make much of an attempt to integrate material across research domains. The implication is that future research should attempt to resolve esoteric issues related to the types of narrowly defined topics highlighted above. Alternatively, as Gottesman concludes in his final chapter, researchers can wait to see if new technologies yield breakthroughs that can guide them to important answers about schizophrenia.

**Empirical Background**

Although our model builds on the ideas and research of other people, our formulation, strongly influenced by our own recent investigations of smooth-pursuit eye tracking, is unique. Our studies, which have been summarized in more detail elsewhere (Iacono & Clementz, 1993), indicate the following:

- Smooth-pursuit eye-tracking dysfunction is bimodally distributed in both individuals with schizophrenia and their first-degree biological relatives (Clementz, Grove, Iacono, & Sweeney, 1992; Iacono, Moreau, Beiser, Fleming, & Lin, 1992). Such a discontinuity in the distribution of eye-tracking performance is consistent with the hypothesis that a single major gene influences pursuit tracking ability.

- Eye-tracking dysfunction is present in only about 50% to 60% of all families with a schizophrenic member (Clementz et al., 1992; Iacono et al., 1992). This finding indicates that eye tracking may not be an informative genetic vulnerability indicator for all cases of schizophrenia.

- Among nonorganic psychotic disorders, deviant smooth-pursuit tracking appears to be specific to schizophrenia and related psychoses (Iacono et al., 1992). Among the relatives of schizo-
with several abnormalities seen in the families of schizophrenics.

Our model has the following genetic components:

- a major gene (or a few genes),
- polygenic factors potentiating or ameliorating effects of the major gene(s), and
- random environmental effects.

Our genetic model is similar to Meehl's (1962), but we conjecture a recessive gene, whereas he supposed dominance. Our conjecture better fits our own data, as well as results summarized by Faraone and Tsuang (1985), who found that single major locus and mixed genetic models postulating a recessive pathogenic gene provided the best data fit.

Our model encompasses several abnormalities seen in schizophrenics' families:

- narrowly diagnosed schizophrenia,
- schizotypal personality,
- eye-tracking dysfunction,
- attentional dysfunction, and
- deficits on neuropsychological tests sensitive to frontal convexity lesions.

We assume that all of these traits are strongly influenced by one gene (or at most a very few strong genes) and also be a collection of individually weak, but collectively important, polygenes. The pleiotropic action of the major gene (i.e., the simultaneous influence of this gene on all of these characteristics) accounts for these traits in schizophrenics and in their relatives, and also for the traits running together in families. We initially conjecture that the major gene is primarily responsible for each abnormality, with the polygenes of distinctly lesser significance.

We emphatically exclude the idea that all (or almost all) clinically schizophrenic individuals have deleterious alleles at the postulated major gene locus. Instead, we propose that only about half of all schizophrenics carry this major gene. The other half of patients diagnosed as schizophrenic have a different disorder, involving different genes or other etiology. Families in which our single gene is operating can be probabilistically identified by the presence of secondary cases of schizophrenia, by relatives having schizotypal features, or by family members showing clear-cut eye-tracking dysfunction. In this respect, our model differs from Meehl's and that of Matthyse, Holzman, and Lange (1986); they proposed a dominant major gene as (nearly) sine qua non for all schizophrenics. By contrast, our model embraces genetic or etiologic heterogeneity. If substantially correct, our model points the way to eventual identification of a discrete cause for a large subgroup of people with schizophrenia.

Our model is testable using modern behavior genetic techniques such as segregation and linkage analysis applied not to schizophrenia families generally, but to the subset of families containing both schizophrenia and eye-tracking dysfunction. An advantage of our genetic model is that our strategy is more economical and efficient than the traditional method for identifying the genetic mechanism underlying schizophrenia. The latter approach is predicated on the use of large samples involving families with multiply affected members. Sample sizes must be especially large if, as many investigators believe, schizophrenia is etiologically heterogeneous. However, as Gottesman has pointed out, few schizophrenics have any affected relatives, a fact that raises questions about the feasibility of the traditional approach and the generalizability of findings (because the results are based on the study of exceptional families). Our research strategy, by focusing on families with both schizophrenia and eye-tracking dysfunction, homogenizes the study sample by including only the 50% of schizophrenics who carry the major gene. It also greatly increases the representativeness and yield of data because we are not dependent on the identification of manifest schizophrenia in family members to test the model. Any patients with living relatives who are willing to undergo a clinical interview and an objective assessment of ocular motor ability would be suitable for our purposes.

Note that our list of indicator traits is not exhaustive. Other traits of interest might include, for example, reaction time crossover (DeAmicis & Cromwell,
Origins of Schizophrenia

1979), sensory gating (Siegel, Waldo, Mizner, Adler, & Friedman, 1984), and span of apprehension (Wagener, Hogarty, Goldstein, Assarnow, & Browne, 1986). The point is that our model can integrate diverse findings of abnormality in schizophrenics and their relatives, and can in principle explain such findings by a relatively simple genetic mechanism. Such a model is eminently falsifiable, is quite extensible, and (not unimportant) also offers a central role for psychologists in the exploration of the genetics of schizophrenia.

REFERENCES


Journal of Nervous and Mental Disease, 167, 593-600.


Commentary to Feature Review

SEARCHING FOR THE ORIGINS OF SCHIZOPHRENIA

Rue L. Cromwell
University of Kansas

In this Commentary, I deal with selected issues concerning the origins of schizophrenia, filling out the picture presented by the books under review. Included are comments on definition, older and enduring notions about origins, some more recent notions, and, finally, some potentially useful but not fully exploited notions. George Bernard Shaw (1907, pp. 140-141) suggested that people are immediately willing to give up an obsolete tool such as a wooden plow or hand-cranked car, but they are most unwilling to give up an obsolete idea or concept. While the concept of schizophrenia does not appear ready to be replaced, some notions about its origins appear worthy of examination.

DEFINITION

Schizophrenia refers to a set of behavioral dimensions that concur in deviant form frequently enough to be referred to as a syndrome or disorder. Yet M. Bleuler has recently reminded us that his father, who coined the term (E. Bleuler, 1911/1950), viewed it as a group of disorders (see Cromwell, in press-a). Most investigators assume a unity, although some suggest plurality (subtyping). Final evidence has not yet been obtained for either view. From a heuristic standpoint, a plural view would indicate that differential defining criteria would point to differential treatment implications, course, and prognosis.

Another issue in the definition of schizophrenia has been the shift away from the relatively existential definition: Bleuler's (1911/1950) definition in terms of associative disturbance, affective splitting, ambivalence, and autistic meaning assignments and the definition of prior editions of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, APA, 1952, 1965) in terms of disturbance in reality relationships. In place of the existential definitions has come the use of operational criteria (APA, 1980, 1987). With this shift, schizophrenia has become objectively defined pri-