At Issue: Assessment of Schizophrenia:
Getting Closer to the Cause

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Abstract

Traditionally, the diagnosis of schizophrenia has depended on the presence of specific behavioral phenomena assessed by way of behavioral observation and patient symptomatic report. Even though the introduction of explicit diagnostic criteria and structured interviews has improved the reliability of schizophrenia diagnosis, it is still unclear how best to define schizophrenia in order to further etiologic research. This situation persists despite ample evidence that schizophrenia is a heritable brain disorder and the existence of laboratory measures that tap into this neurobiological genetic diathesis. We contend that such laboratory measures can be used to supplement traditional clinical assessment in order to improve the definition of schizophrenia, thereby enhancing research into schizophrenia's origins. Ultimately, this increased understanding of the disorder's etiology should facilitate the development of targeted therapeutic interventions.

Keywords: Assessment, reliability, validity, etiology, diathesis, endophenotype.


The face of schizophrenia has changed many times since the days of Kraeplin’s “dementia praecox.” Change is positive and progressive, isn’t it? If the outcome of these changes is evaluated by the principal standards of clinical judgment, reliability, and validity, one might wonder. Reliability can be said to have improved with the introduction of explicit diagnostic criteria and structured interviews. However, the jury is still out when it comes to validity. It is still not known how best to define schizophrenia—that is, how to define schizophrenia so that properly studying identified individuals will uncover the disorder’s etiology. It may be that the focus of assessment on behavioral observation and patient symptomatic report, although essential, is too far removed from the cause of the symptoms to enable precise diagnosis. Uncertainty about what constitutes accurate diagnosis greatly complicates etiologic research and likely contributes to the lack of discovery of a specific causal factor for schizophrenia, despite decades of intensive investigation. This predicament may be remedied by developing an assessment approach that supplements typical symptom-based diagnosis with laboratory measures likely to be more direct manifestations of the genetic pathophysiology of schizophrenia (e.g., psychophysiological deviations, cognitive deficits). These measures are less susceptible to problems that commonly plague clinical assessment, namely the characterization of a syndrome based on consensus expertise, which provides a valuable but imperfect prototype, and the subjective evaluation of symptoms using information gained from often unreliable patient sources.

We are arguing not that conventional diagnostic measures be replaced but rather that they be supplemented with laboratory measures that have been identified as tapping the genetic diathesis for one or more schizophrenia variants. There is now ample evidence from multiple sources that the relatives of schizophrenia patients are deviant on various laboratory measures. It is time to use this information to fuller advantage to assist in the assessment of schizophrenia. As a first step, we recommend more routine inclusion of these measures in schizophrenia...
research protocols. Just as structured interviews are used regularly to assess DSM symptoms of schizophrenia, promising genetically informative laboratory measures should be used whenever possible. And just as specific behavioral symptoms are often related to dependent variables of interest, laboratory measures can be examined for their association with relevant dependent variables. Taking these steps will enhance the understanding of schizophrenia and the associated laboratory measures, ultimately leading to refinements in their application as assessment aids. While future research is warranted, there is considerable emerging evidence supporting the construct validity of many such laboratory measures. This includes demonstrations of moderate to high levels of familial specificity, specificity to underlying central nervous system (CNS) processes shared by different disorders, enhanced sensitivity and reliability, and indications of etiologic relevance.

Just as is the case for traditional symptoms of schizophrenia (e.g., auditory hallucinations and delusions), the specificity of many candidate laboratory measures is low or unknown. However, there is emerging evidence that some laboratory measures demonstrate familial specificity such that deviant performance aggregates in the family members of only patients with a particular diagnosis. While it is true that patients with different diagnoses sometimes show deficits on the same measure, these deficits may represent "phenocopies" that result from acute episodic features or treatment effects (e.g., antipsychotic drugs). However, demonstration of deficits in the well relatives of only one diagnostic group suggests specificity of disorder vulnerability, such as underlying neuropathology. The relatives of schizophrenia patients have been shown to demonstrate impairment on multiple laboratory measures for which the relatives of affective patients, with or without psychosis, demonstrate normal performance (e.g., eye-tracking dysfunction, as reviewed in Levy et al. 1993 and Iacono 1998; and selective cognitive deficits, including impaired memory, Kremen et al. 1998, and attention, Squires-Wheeler et al. 1997 and Kremen et al. 1998). Although the well relatives of schizophrenia patients have been found to be deviant on many laboratory measures, familial specificity has been investigated for only a few measures. Many more empirical investigations comparing the relatives of schizophrenia and nonschizophrenia patients are needed, given that this is a relatively unexplored research area with great potential for informative findings.

In addition to familial specificity, laboratory measures may demonstrate specificity for a biological process or mechanism that is shared by different disorders, thus reducing diagnostic specificity. However, measures that tap a physiological process shared by multiple disorders still provide useful information about disorder vulnerability. For example, prefrontal dysfunction is a well-documented feature of schizophrenia. Consequently, schizophrenia patients have been shown to be impaired on a range of putative frontal lobe cognitive tasks and to demonstrate accompanying abnormalities in cerebral blood flow. New evidence suggests that a functional polymorphism in the catechol-O-methyltransferase gene, a coding region for an enzyme that metabolizes released dopamine, may partially contribute to group differences in frontally mediated cognition and frontal lobe efficiency (Egan et al. 2001). Furthermore, there is evidence that this genetic variation is associated with increased liability for schizophrenia. Even though this liability is unlikely to be specific to schizophrenia, these findings reveal an important mechanism by which genetic differences can be translated into differences in neurochemical regulation and cognitive performance that may, in turn, increase risk for psychopathology. In general, it may be impractical to think that current diagnostic categories are in one-to-one correspondence with nature. The discovery of biological mechanisms underlying psychopathology is more likely to revolutionize psychiatric diagnosis than reveal hundreds of types of unique neuropathological variants, each mapping onto a specific DSM diagnosis.

The sensitivity of laboratory measures equals or exceeds that of many traditional schizophrenia symptoms. For instance, according to a summary derived by Andreasen and Flaum (1991) from six samples of schizophrenia patients, the sensitivity of first rank symptoms ranges from 0.04 to 0.42, with an overall average of 0.21. This is considerably lower than the sensitivity of smooth pursuit eye-tracking deficits (0.45–0.80; Holzman 2000), high antisaccade error rate (0.70; McDowell et al. 1999), and spatial working memory deficits as measured by delayed response tasks (0.71; Snitz et al. 1998).

In addition to having a higher sensitivity, these laboratory measures have the advantage of being more reliably assessed than many traditional schizophrenia symptoms. For instance, Andreasen and Flaum (1991) reported moderate to low median interrater reliabilities for key symptoms such as incoherence (0.57), loose associations (0.57), thought broadcasting (0.48), and bizarre delusions (0.44). Eye-tracking measures typically have interrater reliabilities over 0.90 and have also been shown to have high 9-month to 2-year test-retest reliabilities (Iacono and Lykken 1981; Gooding et al. 1994). There is also evidence for moderate test-retest reliability for some cognitive measures in schizophrenia patients (Park et al. 1999) and their unaffected relatives (Faroane et al. 1999).

Finally, many laboratory measures appear to have etiologic relevance because they are trait characteristics (e.g., remitted patients demonstrate deviant smooth pursuit eye tracking, Iacono et al. 1982; high antisaccade error rates, Curtis et al. 2001; and impaired spatial working memory, Park et al. 1999) that can be measured in well relatives...
(e.g., 25–40% of relatives demonstrate deviant smooth pursuit eye tracking, Holzman 2000; 25–50% high antisaccade error rates, McDowell et al. 1999; and 40–50% impaired spatial working memory, Park et al. 1995). Rather than merely indexing events occurring during an acute psychotic episode (e.g., active psychotic symptoms) or factors associated with chronic mental illness (e.g., medication status, frequent hospitalization), these measures appear to be tapping stable disorder vulnerability. Therefore, they have distinct advantages over traditional symptoms that vary with clinical state and episode. By ignoring measures with demonstrated construct validity, researchers fail to take advantage of valuable tools for refining the definition of schizophrenia, improving diagnostic accuracy, increasing the understanding of the disorder’s etiology through research, and ultimately developing targeted therapeutic interventions.

Defining Schizophrenia: Making Waves or Treading Water?

In the past 3 decades, schizophrenia researchers have used over a dozen diagnostic approaches to define schizophrenia, including four editions of DSM, three World Health Organization ICD systems, and multiple research diagnostic approaches (e.g., CATEGO, Wing et al. 1974; criteria of Feighner et al. 1972; flexible system, Carpenter et al. 1973; RDC, Spitzer et al. 1978). These various diagnostic approaches do not simply provide different ways of identifying the same individuals; they identify different individuals. For instance, in an epidemiologic study of 175 patients succumbing to their first lifetime episode of psychosis, Iacono and Beiser (1992) found that the least restrictive of five diagnostic approaches identified almost three times as many psychotic patients as having schizophrenia as the most restrictive approach. However, all those identified as satisfying the criteria for schizophrenia using the narrowest definition also satisfied the criteria for the broadest definition. This latter finding is important because it indicates that although various diagnostic approaches identify different individuals, narrowly diagnosed schizophrenia identifies a core group of individuals who would be regarded as having the disorder under most diagnostic formulas.

Over this 3-decade span, the criteria that have come to be favored for diagnosing schizophrenia have clearly narrowed. For instance, the once popular schizoaffective subtype of schizophrenia as included in DSM-II (American Psychiatric Association 1968) has been eliminated, as has the notion of “acute” schizophrenia. These changes, most evident in the evolution of the DSM system and now embraced by DSM-IV (American Psychiatric Association 1994), have reduced the likelihood that a psychotic person will receive a schizophrenia diagnosis and have effectively redefined schizophrenia as a chronic disorder. There has also been greater emphasis on the diagnostic significance of bizarre delusions (i.e., beliefs that the person’s culture would regard as totally implausible), negative symptoms (i.e., avolition, affective flattening, and alogia), and compromised social-occupational adjustment. In addition, since the introduction of DSM-III (American Psychiatric Association 1980), the diagnosis of schizophrenia has hinged on ruling out other disorders, most notably affective psychosis.

Although the community of schizophrenia researchers has broadly embraced these changes, demonstrating how the validity of the diagnosis has improved would be difficult. In fact, such a demonstration would necessitate a preconceived notion (or theory) of schizophrenia. For instance, if one believes that schizophrenia is essentially a chronic illness, with a heavy genetic loading and poor outcome, evidence for the validity of narrowly diagnosed schizophrenia can be found (e.g., Cardno et al. 1999; Harrow et al. 2000). However, if one believes that schizophrenia is an episodic disorder that is strongly influenced by psychosocial factors and may include a prominent affective component, acute forms, or variable outcome, the same research findings reduce confidence in modern definitions.

Despite the narrowness of the DSM-IV definition, schizophrenia remains phenotypically heterogeneous. For instance, this diagnosis can be made if the only psychotic symptom is a bizarre delusion, if nonbizarre delusions cooccur with hallucinations, or if in the absence of any delusions or hallucinations only disorganized speech and negative symptoms are present. We know of no research that shows that these phenotypically distinct forms of schizophrenia are likely to be alternate manifestations of the same underlying etiologic process or that schizophrenia is defined as well by one of these phenotypes as it is by the other two. With the possible exception of the paranoid subtype, even the traditional Kraepelinian subtypes of schizophrenia, which further point to its phenotypic diversity, have negligible construct validity.

Many schizophrenia researchers believe that individuals diagnosed with schizophrenia, even under DSM-IV’s narrow criteria, are not only phenotypically heterogeneous but also etiologically heterogeneous. In the worst-case scenario, the situation could be similar to that revealed by research into mental retardation. What was once viewed as a unified syndrome is now known to arise from a range of etiologic causes that vary substantially in the degree to which they are heritable or environmentally determined. Needless to say, the treatment of an etiologically heterogeneous group as a single syndrome has dire consequences for the understanding of what schizophrenia is and how it is best treated. No matter how feverishly scientists search
for the cause(s) of schizophrenia, findings will be confounded by a study sample consisting of members for whom the underlying cause is not the same. In the clinical realm, there is no reason to suppose that two syndromes with similar presentation but different causes would respond to the same treatment or follow the same prognostic course. While it would be premature to treat a person based on the results of a laboratory test alone, ultimately, combining test results with traditional diagnostic signs should enhance the selection of treatment methods. Thus, having the assessment tools needed to identify an etiologically homogeneous schizophrenia group would be highly advantageous.

Resolving Diagnostic Ambiguity: Use of Laboratory Measures as Endophenotypes

The best lead regarding the etiology of schizophrenia stems from well-replicated family, twin, and adoption studies that support a significant genetic predisposition for the development of this disorder (Gottesman 1991). One way to improve homogeneity is to assess traits derived from laboratory measures that are likely manifestations of this predisposition. These traits are endophenotypes—stable, heritable, quantifiable, endogenous characteristics that identify genetic risk. Unlike classic phenotypes, which have been developed by observing and interviewing patients, endophenotypes must be developed using laboratory measurement of traits in the healthy biological relatives of affected individuals. These family members can be expected to share endophenotypic traits that reflect the expression of their shared genes, provided the genes are "switched on" before manifest symptoms develop.

Schizophrenia research has provided ample evidence that predisposing genes are in fact switched on (Cannon et al. 2000a; Erlenmeyer-Kimling 2001). Accordingly, there are deviant characteristics in schizophrenia relatives that serve as candidate endophenotypes, including smooth pursuit eye tracking (Holzman 2000), antisaccade task performance (McDowell et al. 1999), working memory (Park et al. 1995), information processing (Green et al. 1997), and conventional neuropsychological (Cannon et al. 1994, 2000) and cerebral electrophysiological (Freedman et al. 2000) measures. The ideal endophenotype would be highly specific to schizophrenia, thus obviating the need for an interview-based assessment. However, because no single putative endophenotype has this degree of specificity, endophenotypes must be used in conjunction with each other and existing diagnostic criteria to improve classification accuracy and resolve diagnostic ambiguity. The problem of etiologic heterogeneity is in effect sidestepped by first selecting individuals who meet standard criteria for narrowly diagnosed schizophrenia and subsequently focusing on patients who exhibit a given endophenotype. This strategy increases the probability that identified individuals will share the same genetic variant predisposing to schizophrenia.

Endophenotypes offer distinct advantages over the behavioral phenomena upon which traditional psychological assessment depends. Reliance on endophenotypes enhances assessment objectivity and provides a diagnostic sign that tends to be closer to the suspected etiologic cause (e.g., genes, neuropathology) than behavioral displays do. Unlike positive and negative symptoms, which show little evidence of heritability (Cardno et al. 2001), many candidate endophenotypes have been shown to be heritable (e.g., Cannon et al. 2000b; Katsanis et al. 2000; Malone and Iacono 2002). Because endophenotypes reflect the byproduct of genetically influenced CNS processes, finding genes for endophenotypes is likely to provide insights into the etiology of associated disorders. There are already published reports of association between particular endophenotypes and genetic loci, including eye-tracking dysfunction and chromosome 6p (Arolt et al. 1996) as well as the P50 cerebral electrophysiological measure and chromosome 15q (Freedman et al. 1997). Thus, using endophenotypes cuts out some of the factors mediating between cause and outcome, so fewer intervening variables need to be considered and accuracy of classification improves. The following example demonstrates this critical point.

It is likely that brain abnormalities represent an intermediate step between the underlying genetic predisposition to schizophrenia and symptomatic presentation (see, e.g., Meehl 1989). Therefore, cognitive testing may be useful for identifying neuropathological correlates of genetic risk for schizophrenia. Profiles of cognitive deficits may be used to develop an endophenotypic marker that identifies a homogeneous group of individuals with schizophrenia. Over the past 20 years, there has been a proliferation of research indicating neuropsychological deficits in schizophrenia patients and their first degree relatives. Most consistently, these deficits have been in abstraction, auditory attention, and verbal memory (e.g., Faroane et al. 1995). Specific cognitive deficits also provide useful information about the pathophysiology of schizophrenia. For example, spatial working memory is impaired in schizophrenia, perhaps reflecting dysfunction involving the dorsolateral prefrontal cortex (e.g., Park et al. 1995). While standard clinical assessment may detect working memory deficits in schizophrenia patients as they are manifested in disorganized speech or behavior, it is clear that structured neuropsychological examination would more directly and reliably assess this deficit.
Conquering Complacency: Future Directions in Schizophrenia Assessment

Because most researchers agree that schizophrenia is a brain disorder that may be neurodevelopmental in origin, it makes sense to take cues from neurology in designing an assessment plan. For example, in assessing Parkinson’s disorder, multiple levels of information are combined to arrive at a diagnosis. Neurologists gather a history of presenting symptoms such as tremors, rigidity, and bradykinesia; observe behavior such as motoric difficulties and personality changes; may consult with a neuropsychologist to evaluate cognitive changes such as reduced attention span and confusion; and may review imaging results to rule out other neurodegenerative disorders. This should be how psychosis is assessed in the future. It will be imperative that differential diagnoses critical to the accurate assessment of schizophrenia involve the traditional approach, including patient report, behavioral observation, family history of mental illness, and prior medication response, as well as more innovative approaches based on cognitive ability, neuroimaging results, and psychophysiological measures. The results will not only continue to improve diagnostic reliability but also offer a more valid approach to identifying an etiologically homogeneous subgroup of patients. These advances in turn will facilitate research, diagnostic definition refinement, and targeted therapeutic intervention development (e.g., through medications that ameliorate identified physiological dysfunctions or cognitive rehabilitation to combat identified cognitive deficits).

When we talk of the changing face of schizophrenia we are referring to its packaging rather than its core, which has changed little over the past century. By focusing on the core instead of continually rearranging the packaging, researchers have the best chance to make real headway in unraveling schizophrenia’s etiology. When research findings are used to refine the core, one or more neurobiologically homogeneous subsets of individuals with the greatest promise of yielding etiologic insight may be identified.

Toward this end, there are many reasons to be optimistic. Over the past century, important discoveries have been made with regard to crucial pieces of the etiologic puzzle of schizophrenia. Prominent among these findings are the establishment of a genetic basis for schizophrenia, support for dysfunctional eye tracking as an indicator of this genetic diathesis (e.g., Iacono and Clementz 1993), indications that schizophrenia is a neurodevelopmental disorder (e.g., Weinberger 1987), evidence for frontal lobe dysfunction in disorder pathophysiology (e.g., Katsanis and Iacono 1991; Snitz et al. 1998; Conklin et al. 2000), elucidation of attentional disturbances on continuous performance tasks (e.g., Nuechterlein and Dawson 1984), and demonstration of deficient sensory gating as indicated by failure to modulate response amplitude to paired stimuli in startle and event-related potential paradigms (e.g., Yee et al. 1998). Similar deficits are now being identified in well relatives of schizophrenia patients, and meaningful interrelations between these variables are being explored. As the second century of schizophrenia research begins, researchers are armed with new technology, such as high-resolution structural and functional neuroimaging, and the recent mapping of the human genome. The pace of schizophrenia research will likely accelerate.

Over 20 years ago Pope and Lipinski (1978, p. 826) wisely said, “The chronically confused state of research of schizophrenia may partially be owed to an illusory faith in the significance of the symptoms and consequent delay in finding more adequate definitions for its own subject matter.” Are researchers still functioning under the same guise? Has having a reliable diagnostic system encouraged complacency, even though the system may fail to convey meaningful information or capitalize on recent discoveries? For many decades, medical researchers have incorporated empirically substantiated laboratory measures into their disease definitions. Is it not time that psychopathology researchers follow suit?

References


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Minority Research Training in Psychiatry

Through a five-year, $2.5 million grant from the National Institute of Mental Health, the American Psychiatric Institute for Research and Education (APIRE) is seeking through the Program for Minority Research Training in Psychiatry (PMRTP) to increase the number of minority psychiatrists entering the field of psychiatric research.

The program provides medical students with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment, with special attention paid to trainees' career development in research. In addition, stipends are available for a limited number of one- or two-year postresidency fellowships for minority psychiatrists. Residents may engage in full-year research training during the last year of psychiatric residency or in "year off" research training.

Training takes place at research-oriented departments of psychiatry in major U.S. medical schools and other appropriate sites throughout the country. An individual at the site (the research "mentor") is responsible for overseeing the research training experience.

Administered by the American Psychiatric Institute for Research and Education, the program includes outreach efforts to identify minority medical students and residents who are potential researchers and to put them in touch with advisors who counsel them about careers in psychiatric research. Additional activities assist fellows and alumni in their research career development.

The director of the PMRTP is James Thompson, M.D., M.P.H.; the project manager is Ernesto Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees, oversee the research training experiences, and play a role in evaluating the effectiveness of the program.

December 1 is the deadline for applications for residents seeking a year or more of training and for postresidency fellows. For medical students, applications are due three months before training is to begin. Summer medical students who will start their training by June 30 should submit their applications by April 1.

For more information about the PMRTP, call the toll-free number for the PMRTP, 1-800-852-1390, or 202-682-6225, e-mail eguerra@psych.org, or write to PMRTP at the American Psychiatric Institute for Research and Education, 1400 K Street, NW, Washington, DC  20005.