Toward Reformulating the Diagnosis of Schizophrenia

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Objective: The authors assess implications of DSM criteria for schizophrenia by reviewing the criteria's 1) emphasis on psychotic features, 2) dissociation of symptoms from their etiology, 3) exclusive reliance on clinical features but exclusion of biological indicators, and 4) classification of schizophrenia as a discrete category. The authors then discuss alternative conceptions of schizophrenia that take into account recent data concerning its genetic and neurodevelopmental origins and its pathophysiological substrates.

Method: The historical development of diagnostic criteria for schizophrenia is reviewed in the context of recent published data on the biology and development of schizophrenia.

Results: Growing evidence suggests that symptoms of psychosis may be a common end-state in a variety of disorders, including schizophrenia, rather than a reflection of the specific etiology of schizophrenia. Features occurring before the advent of psychosis that are clinical, biological, and/or neuropsychological in nature may constitute evidence of a genetic predisposition toward schizophrenia ("schizotaxia") and may provide more specific information about the genetic, pathophysiological, and developmental origins of schizophrenia.

Conclusions: The success of efforts to treat and prevent schizophrenia will depend to an important extent on an accurate understanding of its causes. This goal can be furthered by conducting field trials to develop research criteria to assess the value of a developmentally sensitive, biologically informed approach to classification that would consider schizotaxia with psychosis (schizophrenia) and schizotaxia alone as distinct diagnostic conditions.

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Schizophrenia has long been recognized as a devastating disorder for patients and their families. Although substantial progress has been achieved both in diagnosis and treatment of the disorder and in understanding the disorder's neurobiological substrates, a full understanding of its origins and pathogenic mechanisms remains elusive. One obstacle to better understanding the causes of schizophrenia may be the current conceptualization of the disorder, as represented by its diagnostic criteria. Despite progress in moving toward the implementation of a scientific psychiatric nosology, the conceptualization of schizophrenia is an issue not easily amenable to empirical resolution (1). DSM-IV and other nosologies provide a foundation for clinical diagnosis, but as various researchers have pointed out (e.g., references 2, 3), there is little basis for regarding DSM's operational definition as the "true" construct of schizophrenia.

This paper considers ways to reformulate the diagnostic criteria for schizophrenia to promote a fuller understanding of the disorder's etiology. The development of diagnostic criteria for schizophrenia in DSM are considered first, with special attention to their emphasis on psychosis. The case for initiating field trials to determine whether biological or neuropsychological criteria should be incorporated into a reformulated research diagnosis is then considered. Throughout the paper, the term psychosis is used to encompass hallucinations, delusions, and/or gross disorganization of thought or behavior.

Diagnostic Criteria for Schizophrenia: Historical Background

Toward the end of the nineteenth century, Kraepelin differentiated dementia praecox and manic-depressive psychoses (4). Dementia praecox described patients who showed a global disruption of perceptual and cognitive processes (dementia) and an early onset (praecox). Kraepelin's dementia praecox patients usually had an illness onset in early adulthood and a progressively deteriorating course with no return to premorbid levels of function. These features contrasted with the relatively intact thinking, later onset, and episodic nature of illness in patients with manic-depressive psychoses, whose episodes of psychopathology alternated with periods of normal function.

Bleuler used Kraepelin's systematic classification of psychoses and a theoretical model of etiological processes to reformulate dementia praecox as schizophrenia, from the Greek words for "splitting of the mind" (5). He described four fundamental symptoms: ambivalence, disturbance of association, disturbance of affect, and a preference for fantasy over reality. To Bleuler, these symptoms reflected schizophrenia's fundamental defect: the separation or splitting of the normally integrated functions that coordi-

nate thought, affect, and behavior. It is noteworthy that two psychotic features emphasized by today's DSM—hallucinations and delusions—were not crucial for Bleuler's diagnosis of schizophrenia.

Bleuler's emphasis on theory as a means for determining the diagnostic relevance of signs and symptoms contrasted sharply with Kraepelin's reliance on empirical observations. Bleuler's approach was also notable for three other reasons. First, his reformulation of dementia praecox as "the group of schizophrenias" foreshadowed the contemporary view that schizophrenia is a heterogeneous group of disorders with similar clinical presentations. Second, Bleuler included defects in affect as a core feature of the disorder. Third, his view of schizophrenia allowed for the possibility of recovery.

Kraepelin's and Bleuler's observations evolved into today's psychiatric classification systems: the ICD and the APA's DSM. In addition to its use of Kraepelin's and Bleuler's views on the signs and symptoms of schizophrenia, the first DSM defined schizophrenia in a way that at least implied environmental causes. For example, all schizophrenic (and other psychiatric) diagnoses included the term "reaction" (as in "schizophrenic reaction, simple type"). Moreover, definitions were vague, did not include specific operational criteria, and did not discuss differential diagnoses. Such imprecise definitions allowed clinicians much discretion in making diagnoses. As a result, in the United States, schizophrenia became the diagnosis of choice for psychotic conditions that lacked a clear "organic" etiology. DSM-II dropped the term "reaction" from its diagnoses and added some discussion of differential diagnoses, but continued the DSM-I tradition of brief, vague descriptions of schizophrenic disorders, without specific operational criteria. Interestingly, both of these early systems viewed psychosis as the key feature of the disorder. DSM-II did contain a category ("schizophrenia, latent type") to describe people with "clear symptoms of schizophrenia but no history of a psychotic schizophrenic episode." This category was intended to encompass individuals with a variety of conditions (e.g., "incipient," "prepsychotic," and "borderline schizophrenia," as well as "schizophrenic reaction, chronic undifferentiated type," from DSM-I). The presence of this category did not detract from the primacy of psychotic symptoms—the term "latent" implied the presence of an underlying or as yet unexpressed psychosis (because psychotic symptoms were absent). It did, however, reflect an important attempt to clarify the role of psychosis in schizophrenic illness.

DSM-III brought about a sea change in psychiatric classification, spearheaded by the "neo-Kraepelinian" movement in the 1960s and 1970s (e.g., references 6, 7) and by investigators in psychiatry and clinical psychology who emphasized the importance of empirical, psychometric validation of psychiatric syndromes (e.g., reference 8). DSM-III contained several innovations, including field tests of diagnostic reliability, specific inclusion and exclusion criteria for diagnoses, multiaxial diagnosis, and a focus on the description of syndromes and course of disorders rather than inferences about their etiology. This latter point made psychiatric diagnosis more explicitly consistent with the diagnosis of other medical disorders of unknown etiology (2, 6).

DSM-III's use of clearly defined criteria limited clinicians' discretion and narrowed the construct of schizophrenia. This development improved the clinical homogeneity of the disorder, better delimited it from other serious mental illnesses, and raised diagnostic reliability to respectable levels. Nevertheless, DSM-III retained the view that psychosis was fundamental to the definition of schizophrenia. The primacy of psychosis in defining schizophrenia also survived DSM-III's revision and its evolution into DSM-IV. Psychosis was de-emphasized in DSM-IV, in that a patient could receive a diagnosis of schizophrenia according to DSM-IV criteria without having delusions or hallucinations. In that case, however, gross disorganization of speech and/or behavior, which are also psychotic symptoms, would still be required because criterion A (i.e., characteristic symptoms) requires at least two of the five symptoms in the category. Thus, four of the five symptoms are still related to psychosis (negative symptoms are the fifth symptom in the category). Moreover, delusions alone can satisfy the criterion if they are bizarre, and hallucinations alone can satisfy the criterion if they involve one or more voices engaging in running commentary or ongoing conversation. (The diagnostic importance of these latter symptoms reflects particularly the influence of Schneiderian concepts, discussed below). Diagnostic changes in DSM-IV thus expanded the nature of the required psychotic symptoms more than they de-emphasized psychosis itself.

The importance of psychotic symptoms in diagnosis extends to other diagnostic systems. Schneider's first-rank symptoms (9), which form the basis of "nuclear schizophrenia," are types of hallucinations and delusions that have come (more than other, "second-rank" symptoms) to characterize the nature of psychosis in the disorder. More important, they have helped to define the disorder itself, although Schneider himself viewed them more as diagnostic tools than as theoretical constructs about the etiology of the disorder (10). First-rank symptoms heavily influenced the development of Research Diagnostic Criteria for schizophrenia, which in turn formed the basis of DSM-III criteria for schizophrenia. These criteria particularly continue to influence ICD-10 in the first three symptoms groups "that have special importance for the diagnosis" of schizophrenia.

Limitations of Current Criteria for Schizophrenia

Stringent, narrow diagnostic criteria for disorders such as schizophrenia were needed in the 1970s and 1980s to

improve the reliability of clinical diagnoses. They were also needed to counteract the prevailing view that mental illnesses were "myths" that harmed patients by stigmatizing them with damaging diagnostic labels. Periodic revisions of the major classificatory systems have continued to refine diagnoses, increase their reliability, and facilitate the adoption of empirical methods to determine which symptoms most appropriately characterized specific disorders. Consequently, communications about, and diagnoses of, mental disorders are far more standardized among mental health professionals and other interested parties (e.g., HMOs, insurance companies, educational institutions) than they used to be, and the rationales for specific diagnostic criteria are much clearer. The reliability of diagnoses provided by recent DSMs has also benefited research to the extent that the clinical characteristics of samples are more standardized across studies and are thus more easily replicated. Moreover, the use of stringent diagnostic criteria laid the groundwork for studies to assess the validity of the concept of schizophrenia, and these studies have in fact demonstrated substantial diagnostic validity. Schizophrenia can be distinguished from other disorders; for example, it shows familial loading and greater levels of functional impairment that may predict larger numbers of recurrent episodes.

Despite the many advances of DSM-III and its successors, further improvement in the classification of schizophrenia is possible. One way to proceed is to consider the "cup" half full rather than half empty and to fill it further by integrating current knowledge with existing conceptual and classificatory schemes. In this context, at least three limitations of the current diagnostic criteria can be addressed: 1) their view of schizophrenia as a discrete category, 2) their emphasis on psychosis, and 3) their use of descriptive attributes and neglect of information about the etiology and pathophysiology of the disorder. Each of these limitations leads to the same question: Can the reliability of the DSM-IV diagnosis of schizophrenia be retained while the validity of diagnosis is increased? These points are addressed in more detail in the following sections.

DSM-IV Schizophrenia Is a Discrete Category

DSM-IV defines schizophrenia, like other disorders, as a discrete category, not a quantitative dimension. Curiously, DSM-IV also states "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" (p. xxii). Despite this qualification, the DSM-IV classification of schizophrenia presents the disorder as a discrete condition.

One implication of this approach, however implicit, is that schizophrenia differs qualitatively from states of health or normalcy. According to this approach, schizophrenia begins with the onset of the symptoms listed in DSM-IV. Before that time, the disorder cannot be validly recognized. If an individual does not have the symptoms of schizophrenia listed in DSM-IV and does not meet the criteria for some other disorder, then no psychiatric diagnosis may be given, although neither clinicians nor researchers would assume necessarily that the individual was normal. However, the failure to meet diagnostic criteria remains potentially consequential. Clinically, it can influence what type of treatment or services a patient receives. From a research perspective, it can determine whether an individual is accepted into a study of schizophrenia or how he or she is classified in a genetic investigation.

In addition, the use of discrete categories raises potential problems for cases in which the symptoms of multiple disorders are present, as it may result in artificial boundaries between conditions and elevated rates of comorbidity (11). Certainly, dimensional models of psychopathology have conceptual and pragmatic limitations as well (11–13). For example, although a variety of studies have identified dimensions that may underlie diagnostic criteria for schizophrenia (e.g., positive, negative, and disorganized symptoms), there are still questions about which dimensions, and how many, should be emphasized (e.g., references 14–17). But the debate about the dimensionality of schizophrenic psychopathology avoids the main question: does a dimensional model more accurately describe the biological nature of schizophrenia? Is it more valid?

A dimensional view of schizophrenia is especially consistent with multigene models of inheritance, and these models provide the best account of the familial transmission of schizophrenia (18, 19). Multigene models assume that multiple genes combine with one another and with environmental factors to cause schizophrenia. Because multiple genes and environmental risk factors are involved, it is possible for people to have low, moderate, or high "doses" of the risk factors that predispose to schizophrenia. People with very high doses are at high risk for schizophrenia, and those with moderate doses may have related conditions such as schizotypal personality disorder, negative symptoms, neuropsychological impairment, or other neurobiologic manifestations of the predisposition to schizophrenia (20).

In fact, a partial foundation for a dimensional view of the biological/clinical manifestations of the vulnerability to schizophrenia already exists in the body of research about "schizotaxia," a term originally introduced by Meehl (21) to describe the unexpressed genetic predisposition to schizophrenia. Meehl suggested that individuals with schizotaxia would develop either schizotypy or schizophrenia, depending on the protection or liability afforded by environmental circumstances. But, in a subsequent revision, he proposed that schizotaxia need not progress into either of these more overt conditions (22). Given current data showing that, in addition to genes, environmental events (e.g., obstetric complications, viruses) augment

susceptibility to schizophrenia, Faraone et al. (23) proposed using the term schizotaxia to indicate the premorbid neurological substrate of schizophrenia. The addition of environmental events to genetic liabilities differs from Meehl's view of schizotaxia, which focused on only the biological consequences of genes. The addition was made because both types of events may occur early in development, interact with each other, and produce neurobiological liabilities for schizophrenia.

More than three decades after the idea of schizotaxia was introduced, a body of research has developed suggesting that it may be a clinically consequential condition. In fact, studies of the nonschizotypal and nonpsychotic relatives of patients with schizophrenia have shown that schizotaxia is not merely a theoretical construct but an actual condition with distinctive psychiatric and neurobiological features. These features include negative symptoms, neuropsychological impairment, deviant eye tracking, and structural brain abnormalities (23). Thus schizotaxia represents both a clinically meaningful condition in its own right and a risk factor for subsequent psychosis.

Schizotaxia is a much broader construct than schizophrenia. Empirical studies suggest that the basic symptoms of schizotaxia may occur in 20% to 50% of first-degree relatives of patients with schizophrenia (20, 24). In comparison, only about 10% of relatives will become psychotic, and less than 10% will develop schizotypal personality disorder (25, 26). These figures suggest that schizotaxia does not lead inevitably to schizotypal personality disorder or to schizophrenia. The view of schizotaxia as a relatively stable condition that does not lead to a more serious disorder in most individuals contrasts somewhat with Meehl's view that it will progress in most people.

Psychosis and the Definition of Schizophrenia

In the DSMs, psychosis has been the sine qua non for schizophrenia (as noted earlier, psychotic symptoms include delusions, hallucinations, and gross disorganization of behavior or thought). But is the level of importance afforded to psychosis appropriate for what research and clinical experience show to be a nonspecific indicator of severe mental illness? An alternative perspective is provided by Crow's theory describing a continuum of psychosis that crosses diagnostic boundaries (15, 27–29). Crow suggested that schizophrenia, schizoaffective disorder, and affective illness exist along one or more such continua. Although he accepted the concept of prototypical entities corresponding to schizophrenia and affective illness, he rejected the idea that they had distinct etiologies. Rather, he suggested that individual disease entities did not actually exist; instead, natural variation along one or more dimensions produced the prototypical disorders. He postulated that a common genetic deficit, located in the pseudoautosomal region of the sex chromosomes, was shared by psychotic disorders, and he hypothesized that genes related to psychosis were responsible for cerebral dominance and the localization of language.

Support for the pseudoautosomal hypothesis is weak (30–32), and a psychosis gene shared by all psychotic disorders has yet to be discovered. Nevertheless, Crow's view of psychosis is intriguing. If, in fact, psychosis has an etiology apart from other core symptoms of schizophrenia, then DSM's diagnostic focus on psychosis in schizophrenia could be a mistake. In the hunt for the causes of schizophrenia, psychosis could be a red herring.

A variety of evidence sustains this view. It is clear that psychosis is not specific to schizophrenia or even to psychiatric disorders. It occurs in neurological disease (e.g., Alzheimer's disease, Huntington's disease, schizophrenia-like psychosis of epilepsy, vascular dementia, and traumatic brain injury), and it can be caused by a range of toxic substances. Beyond the *prima facie* evidence that similar appearing psychoses occur in diverse conditions, Schneiderian first-rank symptoms appear commonly in psychotic conditions other than schizophrenia (33). Moreover, in studies that have used factor analysis, measures of psychosis did not differentiate schizophrenia from other forms of psychopathology (16, 34).

For example, Bell et al. (14) showed that duration of illness and exclusion of affective symptoms correctly classified 97% of first-episode psychosis patients as having DSM-III-R schizophrenia and also correctly identified 97% of such patients who did not have schizophrenia. The inclusion of DSM-III-R's psychosis criterion (criterion A) was not necessary and did not improve the prediction. Serretti et al. (35) obtained a four-factor solution for items on the Operational Criteria Checklist for Psychotic Illness in a large group of inpatients with either DSM-III-R schizophrenia or a DSM-III-R mood disorder. Although they found that two of the factors were more closely related to affective disorders and two were more closely related to schizophrenia, the psychopathology of subjects with schizophrenia overlapped that of patients with bipolar disorder on a "disorganization" factor. The presence of psychotic symptoms among other diagnostic groups has also been described (15, 36), although the issue remains controversial (e.g., reference 37).

Notably, several molecular genetic studies have failed to find linkage to schizophrenia on the basis of the DSM diagnosis but instead found stronger evidence for linkage when other psychotic disorders were included in the phenotype. For example, Maziade et al. (38) failed to detect linkage at 6p24-22 in 18 large multigenerational pedigrees from Eastern Quebec, using either broad or narrow definitions of schizophrenia. However, they did find suggestive evidence in one large pedigree that the locus was associated with vulnerability to both schizophrenia and bipolar disorder when they utilized a broad phenotypic definition that included schizophrenia, schizoaffective disorder,

schizophreniform disorder, bipolar disorder (I and II), and major depression (recurrent).

Moreover, other researchers have suggested that at least one disorder in the schizophrenia spectrum—schizoaffective disorder—might belong to an affective disorder spectrum as well (39). Consistent with this possibility, evidence for linkage has been obtained at this locus (on chromosome 6) for bipolar disorder in Old Order Amish pedigrees (40). Similarly, the chromosome 10p region was implicated for both schizophrenia and bipolar disorder in the NIMH Genetics Initiative pedigrees (41–43).

Wildenauer et al. (44) reported suggestive evidence of linkage to a region on chromosome 18p, by using a sib-pair analysis. Their findings are interesting, partly because they obtained their highest lod scores when they used a broad phenotypic definition that included schizophrenia patients' relatives with bipolar disorder and major depression, in addition to relatives with schizophrenia and schizoaffective disorder. This group recently reported a lod score of 3.1 using this approach and confirmed in principle findings reported by Maziade et al. (38) at chromosome 6p24-22. Moreover, the chromosome region at 18p has also been implicated in bipolar disorder (45, 46).

One explanation for the similarities between psychotic symptoms in different disorders may be the "neurotoxic" effects of psychosis itself. Several lines of evidence are consistent with this possibility. One stems from observations that clinical outcomes of schizophrenia improve when treatment is obtained early in the illness (47). A growing body of evidence has shown that some patients with schizophrenia show neurobiological abnormalities suggestive of a degenerative process, such as enlarged ventricles, loss of tissue volume, degeneration of membrane phospholipids, and/or delayed P300 waves in event-related potential paradigms (48).

This discussion provides support for the view that at least some aspects of psychosis share common elements across disorders, both etiologically and perhaps in their pathophysiological effects as well. It is consistent with Crow's notion of a continuum of psychoses, in regard to their common phenomenology and etiology. It differs from Crow's view, however, in its implications for the construct of schizophrenia. Similarities between psychotic states do not necessarily imply that the underlying disorders lie on the same continuum. An alternative formulation is that psychotic states may impair functioning in a relatively global manner and may have toxic effects of their own. Thus their net effect may be to emphasize superficial similarities between "psychotic" disorders, while obscuring more subtle but defining differences between them.

In summary, at least two problems with the DSM's use of psychosis as a sine qua non for schizophrenia may be identified. Mounting evidence suggests that psychosis is the "fever" of severe mental illness—a serious but nonspecific indicator. Moreover, psychosis is an end-state condition that, in comparison with other indicators, is more distal from schizophrenia's causes and pathophysiology. Because, as we discuss next, more proximal indicators exist, the focus on psychosis may hinder progress in searching for the causes of schizophrenia. This view is consistent with that advanced recently by Andreasen (49), who proposed that clinical symptoms were too variable to define the schizophrenia phenotype and argued instead that the phenotype should be defined by a "more fundamental disruption in mental processes occurring as a consequence of a disruption in neural circuitry" (p. 782).

Separation of Diagnostic Criteria and Concepts of Etiology

A key innovation of DSM-III was its explicit separation of diagnostic criteria from speculation about etiology. At the time DSM-III was developed, this separation was essential because theories of etiology had not yet been subjected to empirical tests. But has DSM-IV, by holding fast to this approach, limited its ability to create more valid diagnoses?

What, for example, would Kraepelin think about the current criteria for schizophrenia? Perhaps he would be pleased that, on the threshold of the twenty-first century, so many of his views have been retained by contemporary nosologists. Or perhaps he might be puzzled that contemporary psychiatrists, unlike their colleagues in other medical fields, are still using signs and symptoms that had been discovered in the nineteenth century.

The point here is simple. DSM's rejection of theoretical speculation about etiology should not lead to the rejection of empirical facts about etiology as being relevant to diagnosis. The puzzle of schizophrenia has not yet been solved, although many pieces of the puzzle are falling into place. Perhaps this empirically validated knowledge about the disorder should be incorporated into diagnostic criteria. If it is not, there exists a significant risk of maintaining a stagnant nomenclature that will not provide a solid foundation for further research.

There is also a risk of a continuing disconnection of treatment from etiology. Since the introduction of antipsychotic medications, pharmacologic treatments have focused on alleviating the most acute, florid symptoms of schizophrenia—i.e., those related to psychosis. Although several newer antipsychotic medications also alleviate selected negative symptoms and cognitive deficits, treatment remains symptomatic. It is not aimed at correcting specific causes of the disorder, nor is it aimed at preventing its onset.

Presumably, knowledge about the etiology of schizophrenia would facilitate the development of more targeted treatment strategies and, possibly, the use of safer treatments. For example, if the causes of schizophrenia were known, there would be no a priori reason why treatments to prevent it would necessarily involve antipsychotic med-

ications. Of course, research on prevention strategies is difficult at the present time, partly because the etiology remains unclear but also because the DSM-IV definition of schizophrenia requires the presence of psychotic symptoms. Consequently, the administration of antipsychotic medications to nonpsychotic individuals with no schizophrenia-related diagnoses is difficult to justify.

An analogy with late-life dementing disorders may be instructive. If vascular dementias and Alzheimer's disease were assessed only when clinical and cognitive deficits had progressed to levels that are moderately severe or greater, then the clinical presentations would look quite similar. Moreover, most treatments would be aimed at reducing the most florid symptoms (e.g., psychosis, agitation, disorganization). On the other hand, if the diagnosis is made when the symptoms are milder, the patterns of impairment will likely differ from each other in ways that better reflect their unique etiologies. If the developmental trajectories of the disorders are also considered, then, at least in the case of vascular dementia, risk factors such as hypertension might be controlled to prevent or modify the course of the disorder itself.

It is certainly counterintuitive to think of psychosis as an end state of schizophrenia. However, there is evidence suggesting that the pathophysiology of schizophrenia is in place long before the first psychotic episode. For example, several researchers have sketched neurodevelopmental models of schizophrenia proposing that some combination of genes and environmental events leads to maldevelopment of the brain as early as the second trimester of life (50–53). This maldevelopment creates a neurodevelopmental syndrome that, as studies of relatives of patients with schizophrenia have shown, can be characterized by neuropsychological, psychophysiological, and neuroimaging measures (23). For reasons that are still unknown, this syndrome sometimes expresses psychosis, and sometimes it does not. Notably, these indicators of the syndrome are more proximal to schizophrenia's initial causes than is psychosis. Could they be useful as diagnostic criteria?

Evidence for a neurodevelopmental theory of schizophrenia comes from several sources. Among these, first, are studies showing higher than expected frequencies of obstetrical complications and prenatal exposure to viruses in individuals who later develop schizophrenia (54). Second, postmortem studies of patients with schizophrenia have shown brain abnormalities indicative of developmental problems in the second or third trimester of pregnancy, such as altered cell migration in the hippocampus, cingulate gyrus, and prefrontal cortex (55). Also, some subjects with schizophrenia show a cavum septum pellucidum (a failure to fuse two laminar membranes), an event that usually occurs in the second or third trimester (56). Third, evidence from a rodent model of perinatal damage (an excitotoxic lesion) to the ventral hippocampus is also consistent with the neurodevelopmental theory. In this model, the rats appear normal until puberty (despite the hippocampal damage) but then develop hyperdopaminergic behaviors (57, 58).

Fourth, there is considerable evidence of neuropsychological deficits, especially in attention, long-term verbal memory, and executive functions (e.g., planning, organizing problem solving, and abstracting) in nonpsychotic, first-degree relatives of patients with schizophrenia (e.g., references 23, 59, 60). Fifth, negative symptoms are frequent among nonpsychotic, first-degree relatives of people with schizophrenia. For example, Tsuang et al. (61) noted that negative symptoms (especially flat affect and avolition), but not positive symptoms, were significantly elevated in schizophrenia families. Odd speech, social dysfunction, and negative symptoms strongly discriminated relatives of patients with schizophrenia from control subjects in the Roscommon family study (62). In contrast, positive symptoms, suspicious behavior, and avoidant symptoms were less discriminating.

Sixth, there is evidence that the neurodevelopmental disorder may be progressive. For example, several studies have provided evidence that enlarged ventricles and decreased tissue volumes were not necessarily related to psychosis (63). In one of these studies, first-episode patients with schizophrenia showed ventricular enlargement and decreased cortical volume, but their intracranial volume did not differ from that of the control group (64). Because intracranial volume is constant after brain growth reaches maximal levels at around 5 years of age (the skull sutures fuse), it is likely that the tissue loss occurred after the pre- and perinatal periods but before the onset of psychotic features. Cannon et al. (65) reported that the nonpsychotic offspring of one or two parents with schizophrenia were more likely than comparison subjects to show sulcal enlargement. Those with two affected parents showed more enlargement than did those with one affected parent. Although ventricular enlargement was also associated with a history of obstetric complications, sulcal enlargement was not. The same group of researchers reported that schizotypal and schizophrenic groups both showed larger ventricles and sulci than comparison subjects (66). The extent of sulcal enlargement did not differ between the (nonpsychotic) schizotypal and schizophrenic groups, but ventricular enlargement was greater in the schizophrenic group.

These studies support the idea that schizophrenic disease begins before the onset of psychosis and expresses itself biologically in characteristic ways. One way to integrate these findings is to conceptualize these factors (e.g., biological abnormalities, biological relatedness to a family member with schizophrenia, selected neuropsychological deficits, and history of obstetric complications) as risk factors for schizophrenia that vary along dimensions of severity. As noted previously, they may also represent components of a clinical syndrome (schizotaxia) that may or may not progress to psychosis. Because many biological or neuropsychological abnormalities start before the onset

of psychosis, but psychosis itself may be associated with neurobiological substrates that are at least partly independent of those related to schizophrenia, studies of schizophrenia could confound antecedent effects of schizophrenia genes with consequent effects of psychosis. To the extent that this confounding occurs, diagnostic criteria that restrict the definition of schizophrenic illness to the onset of psychosis may hinder neurobiological research into its etiological bases.

The value of relatively specific neurobiologic indicators has been demonstrated already in genetic studies. For example, Arolt et al. (67) used deficits in eye tracking as a phenotype and obtained evidence of genetic linkage on chromosome 6p. Freedman et al. (68) used deficits in P50 waves in sensory gating paradigms as a phenotype and obtained evidence in favor of linkage at chromosome 15q13-14. Other abnormalities sensitive to schizophrenia's neurodevelopmental origins—i.e., schizotaxia—include allusive thinking (69), neurologic signs (70), characteristic auditory evoked potentials (71), neuroimaging-assessed brain abnormalities (72), and neuropsychological impairment (73).

The representative studies listed above provide abundant support for the validity of schizotaxia as a concept, but they do not validate schizotaxia as a specific syndrome. To accomplish that goal, field trials will be needed to determine which abnormalities have the requisite reliability, sensitivity, and specificity to warrant inclusion in diagnostic criteria sets. It would be premature at this point to attempt to develop clinical criteria for schizotaxia. Instead, the development of research criteria that could be used to validate (or disprove) the syndrome poses the more immediate challenge.

Reformulating the Diagnosis of Schizophrenia

As the previous discussion suggests, two aspects of the diagnostic criteria for schizophrenia should be reconsidered: their emphasis on psychosis and their reliance on signs and symptoms that are distal to the disorder's etiology and pathophysiology. Such an approach would be a radical departure from tradition, and any changes in the diagnosis will require a strong empirical foundation. The lack of such a foundation has heretofore prevented the inclusion of measures of biological or neuropsychological abnormalities in previous versions of the DSM.

As discussed above, the concept of schizotaxia is especially useful for this purpose. Schizotaxia is still an evolving concept, not a disorder with set criteria. Tsuang et al. (74) recently operationalized research criteria for schizotaxia on the basis of a combination of negative symptoms and neuropsychological deficits, two areas that have been the focus of the most robust findings in first-degree relatives of patients with schizophrenia. To meet the criteria for schizotaxia of Tsuang et al., subjects must show moderate or higher levels of both negative symptoms and neuropsychological impairment. A moderate or higher level of negative symptoms is defined as six scores of 3 or higher on items of the Scale for the Assessment of Negative Symptoms (75). Neuropsychological impairment is defined as two standard deviations below normal in one cognitive domain and at least one standard deviation below normal in a second cognitive domain in tests of attention, long-term verbal memory, and executive function (e.g., planning, organizing problem solving, and abstraction).

These criteria are tentative, and much research will be needed for their refinement and validation. As a preliminary step in that direction, Tsuang et al. reported a treatment study of four adult, first-degree relatives of patients with schizophrenia who met criteria for schizotaxia (74). For inclusion, subjects had to 1) be first-degree relatives of patients with schizophrenia, 2) speak English as a first language, 3) have an estimated IQ score of at least 70, 4) be 19–50 years of age (the age range was partly related to administration of a treatment), and 5) provide informed consent to participate. Exclusion criteria were designed to minimize the influence of comorbid neurological, psychiatric, or other medical conditions (e.g., head injuries, current substance abuse, or history of electroconvulsive treatments) that could mimic symptoms of schizotaxia. Individuals with any lifetime history of psychosis were excluded. Thus the subject's level of clinical symptoms was a significant factor in determining inclusion and exclusion. It is of interest that none of the four subjects met criteria for any other disorder in the schizophrenia spectrum, including schizotypal personality disorder.

It was hypothesized that if schizotaxia in these subjects was biologically related to schizophrenia, then their schizotaxic deficits should respond to risperidone, a medication that improves negative symptoms and neuropsychological dysfunction in patients with schizophrenia (e.g., references 76, 77). Consistent with this prediction, all four cases (and more recently, a fifth case) showed a reduction in negative symptoms and improvement in tests of attention after 6 weeks of treatment with risperidone at a dose range of 0.25–2.0 mg. These results are preliminary and require replication in larger, controlled studies before they can be considered as a basis for treatment. Nevertheless, they imply that in the future, clinical manifestations of schizotaxia may be amenable to treatment before they develop further into a psychotic disorder.

If this conceptualization of schizotaxia is correct, this condition may thus be a more specific expression of the predisposition to schizophrenia than are the DSM-IV criteria for a diagnosis of schizophrenia. Unlike schizophrenia, schizotaxia is not masked by the florid clinical symptoms and neurotoxic consequences of psychosis that are also seen in so many other conditions. But before the concept of schizotaxia can be incorporated into the diagnosis of schizophrenia, its criteria must be validated by demonstrating their predictive and concurrent validity through

field trials. Given the nature of schizotaxia, researchers who are selecting research criteria should consider dimensional as well as categorical criteria. The criteria would presumably reflect the biological and clinical alterations that occur before the advent of psychosis. This approach would broaden the diagnosis of schizophrenia into two categories—schizotaxia and schizotaxia with psychosis (schizophrenia), a categorization analogous to the classification of depression. In this formulation, schizotaxia with psychosis would be equivalent to the DSM-IV conceptualization of schizophrenia. Schizophrenia without psychosis would be equivalent to schizotaxia.

Some might argue against this position by claiming that the distress and disability associated with schizotaxia do not reach levels that would qualify the condition as a disorder, although many clinical and neurobiologic features of schizotaxia, such as cognitive deficits in attention, are well described. Existing research provides little data about the functional implications of schizotaxia or about whether treatment is indicated. Investigation of the functional implications of the syndrome is clearly a direction for future research.

An additional problem is that, given the current state of knowledge, preventive treatments cannot yet be offered to people with schizotaxia. Because most cases of schizotaxia would not progress to schizophrenia, treatment would not be warranted in the absence of evidence for clinically meaningful impairments. Yet, if efforts at developing preventive interventions are to be taken seriously, it follows that, someday, diagnostic and therapeutic technologies will reach a point where ethical and effective treatments of schizotaxia will be possible.

A final problem is that use of the category of schizotaxia risks dramatically increasing the numbers of people who are stigmatized with the label of a psychiatric diagnosis. This possibility may have a variety of implications, some of which are difficult to predict. A diagnostic label of schizotaxia may affect both how other people react to those with the condition and may also affect their view of themselves. The use of this term could prevent some individuals from getting health insurance coverage, because they would be deemed high-risk cases. This latter problem is less worrisome, as it could be solved with the type of legislation that now protects people for whom genetic testing has revealed a high risk for other illnesses (78). The other problems underscore the potential importance of genetic counseling and psychotherapy to help individuals and families cope with the information that they meet criteria for schizotaxia. Clearly, there is a need for ethical inquiry to help balance the ills wrought by stigma with the need to improve diagnostic nomenclature in a manner that will someday be relevant for preventive research and intervention (i.e., when schizotaxia genes and genetic and environmental risk factors for psychosis are identified). Moreover, concerns about applying a diagnosis of schizotaxia (which unlike a diagnosis of schizophrenia, does not denote psychosis) will need to be balanced against the potential treatment benefits associated with the identification of people with significant clinical problems.

Whether the term schizotaxia or some other expression is used, nosologists will need to address both the nonspecificity of psychosis and the existence of a syndrome that has a biological connection with schizophrenia. The necessity of doing so will become acute after the field develops interventions that will prevent psychosis among people with schizotaxia.

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