Basic research

Conceptualization of the liability for schizophrenia: clinical implications

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Although substantial progress has been achieved in both the diagnosis and treatment of schizophrenia and the understanding of its neurobiological substrates, a full understanding of its origins and pathogenic mechanisms remains elusive. Understanding the development of schizophrenia is critical for developing new treatment strategies, in part because early interventions—ie, secondary prevention—are associated with better treatment outcomes. There is thus a growing emphasis on the accurate diagnosis of schizophrenia as soon as symptoms of psychosis are evident. Conceptually, of course, the most effective treatment would involve the prevention of psychosis altogether—ie, primary prevention.

Progress towards this goal, however, remains in its infancy, in part because we are only just learning to identify what the genetic liability to schizophrenia looks like before the onset of psychosis. In this paper, we discuss recent progress in this area by focusing on "schizotaxia," a clinically meaningful condition that may reflect the liability for schizophrenia. We then consider an important implication of identifying this condition: the possibility of treatment strategies for the primary pre-

Historically, the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for schizophrenia have emphasized several features, including symptoms of psychosis, a dissociation of symptoms from their etiology, a reliance on clinical symptoms, and a categorical approach to classifying the disorder. Although these emphases are quite useful, they have limitations. We review these here, and stress the importance of incorporating recent data on the genetic/biological and neurodevelopmental origins of schizophrenia into current conceptions of the disorder. We also review "schizotaxia," which is a concept that embodies this point of view, occurs before the onset of psychosis, and is hypothesized to represent the liability for schizophrenia. If our hypothesis on this point is correct, the identification of schizotaxic individuals will eventually facilitate the development of prevention strategies by identifying a premorbid (but clinically significant) condition for schizophrenia. Moreover, the identification of biological or neuropsychological components of schizotaxia will provide more specific bases for developing novel treatment interventions. Our initial attempts to develop protocols for the assessment and treatment of schizotaxia are encouraging, and will be reviewed.

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vention of schizophrenia. The development of the notion of schizotaxia, however, begins with a review of how schizophrenia has been classified over the last century, especially in regard to the diagnostic emphasis on symptoms of psychosis, the view of schizophrenia as a discrete category, and the dissociation of clinical symptoms from their underlying genetic/biological etiologies. Limitations of these approaches are then considered, followed by ways in which genetic research has helped to focus attention on phenotypic expressions of schizophrenia genes (ie, schizotaxia) before the onset of psychosis. Finally, clinical implications of schizotaxia are considered.

The classification of schizophrenia: historical background

In 1895, Kraepelin distinguished dementia praecox from manic-depressive psychoses.[1] Dementia praecox referred to patients with global disruptions of perceptual and cognitive processes *(dementia)*, and early onsets *(praecox)*. These patients usually showed an onset in early adulthood, and a progressively deteriorating course that did not include a return to premorbid levels of function. In contrast, manic-depressive features included relatively intact thinking, a later onset, and an episodic course in which episodes of psychopathology alternated with periods of normal function.

Eugen 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."[2] His reasoning was that the defects in thinking in schizophrenia were not identical to those occurring in dementias associated with aging, for example, but instead reflected deficits of "association." Bleuler described four basic symptoms: ambivalence, disturbance of association, disturbance of affect, and a preference for fantasy over reality. To Bleuler, these reflected schizophrenia's fundamental defect: the disassociation or splitting of the normally integrated functions that coordinate thought, affect, and behavior. It is important to note that, in contrast to subsequent *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, Bleuler's diagnosis of schizophrenia did not depend on psychotic features such as hallucinations and delusions.

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 other reasons. First, his reformulation of dementia praecox as "the group of schizophrenias" foreshadowed the modern 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 remission or recovery.

Kraepelin's and Bleuler's observations provided the foundation for contemporary systems of psychiatric classification, including the *International Classification of Disease and Death* (ICD) and the American Psychiatric Association's DSM. These systems have thus benefited from incisive clinical observations of, and conceptualizations about, schizophrenic illness. They also, however, inherited the limitations of Kraepelin and Bleuler's efforts at classification and diagnosis. The first DSM definition of schizophrenia was vague, unreliable, and allowed for too much discretion on the part of clinicians. As a result, apparent geographical differences arose in the rates of schizophrenia. In the United States, schizophrenia became the diagnosis of choice for psychotic conditions that lacked a clear "organic" etiology, and thus appeared to occur more frequently than it did in the United Kingdom.[3] DSM-II continued the DSM-I tradition of unreliable diagnoses, although it did incorporate the issue of differential diagnoses. Both of these early systems viewed psychosis as a key feature of the disorder (we use the term psychosis to encompass hallucinations, delusions, and gross disorganization of thought or behavior). Interestingly, however, and despite its emphasis on psychosis, DSM-II did contain a nonpsychotic subtype of schizophrenia, called latent schizophrenia, which included a heterogeneous group of patients who in DSM-I were diagnosed with "incipient" or "borderline" schizophrenia, among other conditions. As the term "latent" implies, however, the category was intended to encompass individuals with underlying or occult psychotic conditions, instead of identifying individuals who had schizophrenia in the absence of psychosis. Nevertheless, the category did represent an important attempt to delineate the role of psychosis in schizophrenia.

DSM-III resulted largely from the efforts of the "neo-Kraepelinian" movement of the 1960s and 1970s,[4] and from the efforts of other investigators in psychiatry and clinical psychology who argued for empirical, psychometric validation of psychiatric syndromes (eg, reference 5).

DSM-III represented a marked shift from previous DSMs, and contained a number of innovations, like 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 uncertain etiology.[6,7]

DSM-III's use of clearly defined criteria narrowed the construct of schizophrenia and in so doing improved its diagnostic reliability. This improved the clinical homogeneity of the disorder and facilitated its delineation from other serious mental illnesses. Still, DSM-III retained the position that psychosis was fundamental to the definition of schizophrenia, as Criterion "A" required an hallucination or delusion at some point in the illness. Similarly, Criterion A in DSM-III-R required "characteristic psychotic symptoms." In the latter revision, the type of psychotic symptoms required for the diagnosis was broadened to include gross behavioral disorganization (eg, incoherence, catatonia, and grossly inappropriate affect), although types of hallucinations or delusions, by themselves, sufficed to meet the Criterion.

In DSM-IV, Criterion A could be met through a combination of delusions, hallucinations, and gross disorganization (of speech and/or behavior). Because 4 out of 5 symptoms are related to psychosis (negative symptoms are the 5th symptom in the category), and Criterion A requires at least 2 out of 5 symptoms, psychosis remains necessary for the diagnosis of schizophrenia. Moreover, delusions alone are enough to satisfy the Criterion if they are bizarre, as are hallucinations, if they involve one or more voices engaging in running commentary or ongoing conversation. Thus, recent changes in DSM criteria have expanded the nature of the psychotic symptoms required for diagnosis, but have retained the emphasis on psychosis in the construct of schizophrenia.

Although the evolution of the DSM is emphasized here to trace the importance of psychosis in diagnostic classifications of schizophrenia, symptoms of psychosis—especially delusions and hallucinations—are also core features of ICD diagnostic criteria. The ICD-10 diagnosis of schizophrenia, for example, is heavily influenced by the Schneiderian concept of "nuclear" schizophrenia, which involves First-Rank Symptoms. As is well known, these symptoms center on types of delusions and hallucinations.[8]

Limitations of the current view of schizophrenia

It is now generally agreed that stringent, narrow diagnostic criteria for schizophrenia and other mental disorders 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 refined diagnoses further, increased their reliability, facilitated the task of differential diagnosis, and provided the basis for 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 than they used to be, and the rationales for specific diagnostic criteria are much clearer. The reliability of diagnosis provided by recent DSMs has also benefited research to the extent that the clinical characteristics of samples are more standardized across studies and thus are more easily replicated. Moreover, the use of stringent diagnostic criteria laid the groundwork for studies to assess the validity of the concept. In fact, the "modern" view of schizophrenia (DSM-III and later) also has diagnostic validity. It can be delineated from other disorders; for example, it shows familial loading, and it predicts outcome (greater levels of functional impairment predict larger numbers of recurrent episodes).

Despite the many advances of DSM-III and its successors, however, we may still consider how the classification of schizophrenia could be improved further. This is not intended as a criticism of our progress thus far, but instead reflects the need to modify our conceptual and classificatory schemes as new information becomes available. In this context, at least three limitations of the current diagnostic criteria may be addressed, including: its emphasis on psychosis, its definition of schizophrenia as a discrete category, and its dissociation of symptoms from their etiology. Each of these limitations leads to the same issues: can the validity of the diagnostic criteria for schizophrenia be increased while its reliability is retained? More specifically, is the current classification of schizophrenia the most accurate reflection available of the biological condition that pro-

duces it? Perhaps most importantly from a practical point of view, would alternative conceptions of schizophrenia promote the development of novel treatment strategies? We address these issues, first, by revisiting the issue of psychosis.

Psychosis and the definition of schizophrenia

As the previous discussion of DSM diagnostic criteria emphasized, psychosis has long been the sine qua non for schizophrenia. But is psychosis really a specific component of schizophrenia, or is it more of a nonspecific indicator of severe mental illness? A variety of evidence supports the latter view. It is clear that psychosis is neither specific to schizophrenia, nor even to psychiatric disorders. It occurs, for example, in neurological disease (eg, Alzheimer disease, Huntington disease, schizophrenia-like psychosis of epilepsy, vascular dementia, and traumatic brain injury) and can be caused by a range of toxic substances or impaired metabolic states. Even Schneiderian first-rank symptoms, which have played such a prominent role in defining the nature of psychotic symptoms in modern diagnostic systems, are not specific to schizophrenia.[9] Similarly, several recent factor-analytic studies showed that measures of psychosis in schizophrenia did not differentiate it from other forms of psychopathology.[10,11]

Bell et al,[12] for example, 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 to achieve these levels of sensitivity and specificity, nor did they improve the prediction. Serretti et al[13] obtained a 4-factor solution for items on the Operational Criteria Checklist for Psychotic Illness among a large sample of DSM-III-R inpatients having either schizophrenia or a mood disorder. Although they found that two of their factors were more closely related to affective disorders and two were more related to schizophrenia, the psychopathology of subjects with schizophrenia overlapped that of bipolar patients on a "disorganization" factor. Psychotic symptoms among other diagnostic groups have also been noted,[14,15] although the issue remains controversial (eg, reference 16).

Notably, several molecular genetic studies failed to find linkage to schizophrenia on the basis of the DSM diagnosis, but instead showed stronger evidence for linkage when the phenotype was broadened to include additional psychotic disorders (eg, Maziade et al[17] at chromosome 6p and Wildenauer et al[18] at chromosome 18p). Results from other genetic studies have also added to converging evidence that different psychotic disorders share common elements.[19] For example, at least one disorder in the schizophrenia spectrum—schizoaffective disorder—might belong to an affective disorder spectrum as well.[19,20] Consistent with this view, schizoaffective disorder occurs in families with either schizophrenia or affective disorders. More generally, both schizophrenia and affective disorders occur at elevated rates in families with either disorder (eg, reference 21). Moreover, evidence for genetic linkage for both types of psychotic disorder has been obtained at similar chromosomal loci. Ginns et al,[22] for example, obtained evidence for linkage at 6p for bipolar disorder in Old Order Amish pedigrees, near the same region that Maziade et al, and others, have identified.[23] Similarly, the chromosome 10p region was implicated for both schizophrenia and bipolar disorder in the National Institute of Mental Health (NIMH) Genetics Initiative pedigrees,[24-26] and regions in 13q and 18p were also implicated recently in both of these disorders.[19]

One rationale for the similarities between psychotic symptoms in different disorders may involve inherent pathophysiological effects of psychosis. Several lines of evidence support this possibility. One stems from observations that clinical outcomes of schizophrenia improve when treatment is obtained early in the illness.[27] Another involves the growing body of evidence that some patients with schizophrenia show neurobiological abnormalities, such as enlarged ventricles, loss of tissue volume, degeneration of membrane phospholipids, and/or delayed P300 waves in event-related potential paradigms.[28] Recently, evidence consistent with the possibility of common neurobiological mechanisms across psychotic conditions has emerged, involving, for example, abnormal γ-aminobutyric acid (GABA)-ergic neurotransmission.[29]

Thus, similarities in psychotic symptoms in different disorders may be apparent at multiple genetic and (other) biological levels, as well as phenomenologically. What are the implications of such similarities? Crow proposed a continuum of psychosis that crosses diagnostic boundaries,[30-32] and suggested that schizophrenia, schizoaffective disorder, and affective illness exist along one or

more such continua. While he accepted the view that prototypical entities corresponded to schizophrenia and affective illness, he rejected the idea that they had distinct etiologies. Instead, he hypothesized that 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 hypothesized further that genes related to psychosis were responsible for cerebral dominance and the localization of language.

Support for the pseudoautosomal hypothesis is weak,[33-35] 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 the 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.

The foregoing discussion of common elements in psychoses is consistent with Crow's notion of a continuum of psychosis, in regard to its 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 view is that since psychotic states may impair functioning in a relatively global manner, and may have adverse neuropathological effects of their own, their net effect may be to emphasize superficial similarities between such disorders, while obscuring more subtle, but defining, differences between them.

In summary, we see two problems with the use of psychosis as a sine qua non for schizophrenia. First, mounting evidence suggests psychosis may be the "fever" of severe mental illness. While it is a serious problem, it is a nonspecific indicator. Second, psychosis is an end-state condition that, in comparison with other indicators, is a relatively distant consequence of schizophrenia's causes and pathophysiology. If these views are correct, then the focus on psychosis may actually hinder progress in searching for the causes of schizophrenia. In the next two sections, we discuss additional limitations of the diagnostic focus on psychosis, and consider alternative conceptualizations of schizophrenic illness.

DSM-IV schizophrenia is a discrete category

Like other disorders, DSM-IV defines schizophrenia as a discrete category rather than a quantitative dimension, despite its qualification that "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, DSM-IV)*.

An implicit implication of this approach is that schizophrenia differs qualitatively from states of health or normalcy. This idea holds that schizophrenia begins with the onset of its symptoms as listed in DSM-IV. Before that time, the disorder cannot be recognized validly; if the criteria for other disorders are also not met, individuals cannot receive any psychiatric diagnoses. To a significant degree, the "cut point" for making the decision is whether psychotic symptoms are present or not.

In general, a reliance on discrete categories raises potential problems for cases that share symptoms of multiple disorders, because they may lead to artificial boundary categories and elevated rates of comorbidity.[36] Certainly, dimensional models of psychopathology have conceptual and pragmatic limitations as well.[37] For example, although a variety of studies have identified underlying dimensions of the diagnostic criteria for schizophrenia, (eg, positive, negative, and disorganized symptoms), both the number and the content of these dimensions remain unclear.[38] These concerns are significant, but the question remains as to whether a dimensional model describes the biological nature of schizophrenia more accurately than a categorical one? Is it more valid?

Certainly, a dimensional view of schizophrenia is more consistent (than a categorical one) with polygenic models of inheritance, which is the model that provides the best account of the familial transmission of schizophrenia.[23,39] Polygenic 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 risk factors that predispose to schizophrenia. People with very high doses are at high risk for schizophrenia, those with moderate doses may have related conditions such as schizotypal personality disorder, negative symptoms, neuropsychological impairment, or other neurobiological manifestations of the predisposition to schiz-

ophrenia.[40] It is clear that, in this view, a dimensional model describes the range of schizophrenic illness better than does a categorical one.

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[41] 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, although he later proposed that schizotaxia need not progress into either of these more overt conditions.[42] Given current data showing that, in addition to genes, environmental events (eg, obstetric complications, viruses) augment susceptibility to schizophrenia, Faraone et al[43] proposed that we use the term schizotaxia to indicate the premorbid, neurobiological substrate of schizophrenia.

Now, almost 40 years after the idea of schizotaxia was first advanced, a preponderance of evidence shows it to be a clinically meaningful condition. In fact, studies of nonschizotypal, nonpsychotic relatives of schizophrenic patients show that schizotaxia is not merely a theoretical construct, but has distinct psychiatric and neurobiological features. These include negative symptoms, neuropsychological impairment, impaired eye-tracking, and structural brain abnormalities.[43]

Schizotaxia is a broader construct than schizophrenia. Our empirical studies suggest that the basic symptoms of schizotaxia occurs in 20% to 50% of first-degree relatives of schizophrenic patients.[40,44] In comparison, only about 10% of relatives will become psychotic, and less than 10% will develop schizotypal personality disorder.[45,46] These figures suggest that schizotaxia does not lead inevitably to schizotypal personality or schizophrenia, but in most cases is a long-term condition. This leads to the question of what type of etiological model accounts best for a long-term biological vulnerability (schizotaxia) that, under some circumstances, leads to more serious conditions (schizophrenia).

Diagnostic criteria for schizophrenia ignore its etiology and pathophysiology

DSM-III (and later versions) explicitly dissociated diagnostic criteria from speculation about etiology to avoid incorporating theories of etiology that were not subjected to empirical tests. At this point, however, DSM-III's rejection of theoretical speculation about etiology should not lead us to reject empirical facts about etiology as being relevant to diagnosis or conceptualization. Moreover, such a view risks a continuing disconnection of treatment from etiology. Since the introduction of antipsychotic medications, pharmacological treatments have focused on alleviating the most acute, florid symptoms of schizophrenia, ie, 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.

We recognize how counterintuitive it is to think of psychosis as a somewhat nonspecific end state of schizophrenia. But consider the evidence suggesting that schizophrenia's pathophysiology is put into place long before the first psychotic episode. Many researchers have sketched neurodevelopmental models of schizophrenia based on adverse genetic and environmental interactions occurring as early as the second trimester of life (see, eg, refs 47-55). These events create a neurodevelopmental syndrome, which, as studies of relatives of schizophrenic patients have shown, is characterized by neuropsychological, psychophysiological, and neuroimaging abnormalities.[43] Evidence for neurodevelopmental syndromes in schizophrenia is extensive at this point, and emphasizes clinical, biological, and neuropsychological abnormalities, both in individuals who later develop schizophrenia, and in their nonpsychotic biological relatives. For reasons that are still unknown, this syndrome sometimes leads to psychosis, and sometimes does not. Notably, these indicators of the syndrome are more proximal to schizophrenia's initial causes than is psychosis.

Clinical implications

Schizophrenia as a premorbid condition

Taken together, the evidence described above supports 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 its manifestations (eg, biological abnormalities, biological relatedness to a family mem-

ber with schizophrenia, selected neuropsychological deficits, and history of obstetric complications) as risk factors that vary along dimensions of severity, for schizophrenia. Schizotaxia describes this premorbid, yet clinically significant, neurodevelopmental condition. Psychosis, in contrast, represents a relatively less specific consequence of schizophrenic disease than does schizotaxia. If our view is correct, then the clinical significance of schizotaxia is related to both its (putative) status as a discrete condition, and its status as a risk factor for schizophrenia.

The emphasis on prepsychotic aspects of schizophrenic illness, ie, schizotaxia, has potentially significant implications for the treatment of schizophrenia. For one, the identification of a premorbid condition, especially one that is itself significant clinically, will facilitate the development of early intervention strategies. Cameron (cited in ref 56) first described, in 1938, the need to treat schizophrenia early to prevent subsequent deterioration. As noted earlier, evidence has since accumulated to support the view that the longer treatment is delayed, the poorer the subsequent prognosis.[27,57,58]

Other benefits of early treatment are also likely, such as the delay or prevention of the social, interpersonal, cognitive, and affective disruptions that accompany and follow an initial psychotic episode. One potential consequence of secondary prevention is simply the delay of onset. This may be especially valuable for early-onset cases because these patients would then have more time to mature before having to cope with a serious and chronic illness. Moreover, untreated schizophrenia may become more resistant to treatment, in part because psychosis itself may create or lead to widespread neurobiological abnormalities[28] that make treatment more complicated and difficult.

The case for preventive treatment

Research and theory about the early treatment of psychosis naturally leads to the question: can psychosis be avoided? That is, can schizophrenic illness be treated before psychosis is added to it? Most researchers have approached the issue of primary prevention by focusing on prodromal symptoms as indicators of an impending psychotic disorder, but such symptoms are often nonspecific. McGorry et al[59] showed, for example, that DSM-III-R prodromal symptoms for schizophrenia occurred in 15% to 50% of high-school students. This raises obvious questions about the validity—and wisdom—of intervening on the basis of such symptoms. Are prodromal indicators like social withdrawal or subtle changes in thinking or affect valid enough indicators of early schizophrenia to warrant intervention, which may involve powerful antipsychotic medications and their associated side effects? Is the cost/benefit analysis favorable enough to risk the potential anxiety and stigmatization (for both "patients" and their families) that will likely attend the classification of an individual as at-risk for schizophrenia, probably in the near future? Unfortunately, these questions cannot yet be answered in the affirmative. In part because prodromal symptoms that are specific to schizophrenia (or to other psychotic illness) are still unknown,[60] the application of primary prevention programs appears premature in the absence of clear clinical symptoms.

Among the steps that will make prevention efforts more feasible for nonpsychotic individuals are, first, to identify the population at risk, and second, to develop a rationale for treatment. We propose that the study of schizotaxia will help to achieve this goal. Given this hypothesis, what are the next steps that must be taken to design a strategy aimed at preventing schizophrenia? Clearly, the validity of schizotaxia as a predictor of subsequent schizophrenia must be firmly established.

As Robins and Guze[5] pointed out, it is crucial to establish both the concurrent and predictive validity of putative syndromes. Does the classification of schizotaxia predict neuropsychological, neuroimaging, or psychophysiologic findings that are consistent with what is known about the neurobiology of schizophrenia? As we have reviewed elsewhere, a growing body of literature suggests that the answer is "yes."[43] Abnormalities found among relatives of schizophrenic patients include eye-tracking dysfunction,[61] allusive thinking,[62] neurologic signs,[63] characteristic auditory evoked potentials,[64] neuroimaging-assessed brain abnormalities,[65] and neuropsychological impairment.[66]

More importantly, does schizotaxia predict the subsequent emergence of psychotic symptoms or other forms of psychopathology? Studies of children at risk for schizophrenia show that features of schizotaxia do predict subsequent schizophrenia and related disorders (refs 67-70 and Erlenmeyer-Kimling L, 1997, personal communication). Nevertheless, more work is needed to create measures of schizotaxia that will accurately classify children who do and do not go on to develop schizophrenia.

Basic research

The schizotaxia treatment protocol

Although schizotaxic features cannot yet be used to select preschizophrenic children for primary prevention protocols, our current knowledge about schizotaxia suggests a method for evaluating medications that may someday be useful for the prevention of schizophrenia. This method, which we call the "schizotaxia treatment protocol" is straightforward: select a sample of schizotaxic first-degree relatives of schizophrenic patients and, using standard randomized clinical trial methodology, determine if a putative preventative treatment modifies the features of schizotaxia in an acute trial. Presumably, any medicine that mitigates the features of schizotaxia will be a reasonable candidate for a primary prevention trial when such trials are possible.

The use of the schizotaxia treatment protocol assumes that the syndrome of schizotaxia observed among first-degree relatives of schizophrenic patients shares etiologic and pathophysiologic pathways with preschizophrenic subjects. If this assumption is true, then any medication that targets these pathways to mitigate schizotaxic features may also work to reduce the likelihood of the onset of psychosis. This assumption is reasonable because: (i) first-degree relatives of schizophrenic patients are at high risk for carrying schizophrenia susceptibility genes,[39] and (ii) the features of schizotaxia observed among these relatives are similar to those seen in children who eventually become schizophrenic.[43]

A major advantage of the schizotaxia treatment protocol is that it can avoid some of the ethical issues raised by primary prevention studies of schizophrenia. Prevention studies will label children and adolescents as potential future schizophrenics. As noted above, this opens up the possibility of stigmatization and psychological harm to the subject and their families. It is also possible that medications chosen for prevention trials may pose greater risks to children and adolescents than adults. That would preclude their use in the absence of a solid rationale for efficacy. But, because schizotaxia can be defined in the adult relatives of schizophrenic patients, using an acute schizotaxia trial for putative preventative medicines will not require studies of children or adolescents.

If successful treatments are developed and tested, and the syndrome of schizotaxia is validated, then treatments at earlier ages may be considered. For example, if an acute schizotaxia treatment trial in adults is successful, one might consider an acute trial for adolescents. If an adolescent trial were to be successful, then we might consider a trial to prevent psychosis (assuming that the target, preschizophrenic population could be accurately defined).

One of the difficulties with implementing the schizotaxia treatment protocol is the lack of a consensual definition of schizotaxia. Although we can make many measurements of schizotaxic features (eg, neuropsychological symptoms, negative symptoms, social functioning), the field has yet to agree on how these measures should be combined to create a schizotaxic category.

Tsuang et al[71] recently described a working definition of schizotaxia based on a set of specific criteria for the purpose of developing a treatment protocol. In this initial approach, we diagnosed schizotaxia in people who met the following criteria:

- They had at least one relative with schizophrenia;
- They had estimated IQs of 70 or higher;
- They had none of the following: lifetime history of psychotic disorders; substance abuse diagnosis within 6 months of diagnosis; head injury with documented loss of consciousness exceeding 5 minutes (or subsequent cognitive deficits); history of neurologic disease or damage; medical condition with significant cognitive sequelae; or a history of electroconvulsive treatment;
- They had at least moderate levels of negative symptoms, defined as 6 items rated 3 or higher on the Scale for the Assessment of Negative Symptoms (SANS[72]);
- They had moderate or greater deficits (defined as approximately two or more standard deviations below appropriate norms) in at least one of three cognitive domains: vigilance/working memory, long-term verbal memory, and executive functions;
- They were at least one standard deviation below normal in a second cognitive domain (see ref 71) for lists of specific tests and measures on tests used to meet the neuropsychological criteria).

Our decision to require moderate deficits in different domains ensured that our initial treatment attempts would include only adults with demonstrable clinical and neuropsychological difficulties. This was important to demonstrate both the clinically meaningful nature of schizotaxia, and also to make the risk/benefit assessment of treatment more favorable.

Our first application of the schizotaxia treatment pro-

tocol[71] used risperidone, a novel antipsychotic medication. As we noted above, trials of these medications would appear reasonable on the basis of our assumption that individuals with schizotaxia share etiological and psychopathological elements with schizophrenia. Trials with the older, typical antipsychotics, however, were limited by reluctance to use these medications in nonpsychotic populations, mainly because of their side effects and subsequently high rates of noncompliance,[73] but also because of their essential inability to alleviate negative symptoms[74] or neuropsychological deficits.[75]

Another reason we chose risperidone was that, compared with other novel antipsychotic medications, it had (at the inception of the study) been shown to reduce positive and some negative symptoms in schizophrenia.[74,76,77] It was clearly safer than typical neuroleptics, in that it produced fewer extrapyramidal side effects (at least at lower doses, eg, refs 74, 77). Notably, it also improved cognitive functions in schizophrenia, especially in attention or working memory,[76,78,79] but possibly in verbal long-term memory[79] and executive functions[76] as well. This latter feature was especially important given that neuropsychological impairment is a hallmark of schizotaxia.

Based on these issues, we began an open trial of risperidone in people who met our criteria for schizotaxia.[71] After all entrance criteria were met, subjects received low doses (starting at 0.25 mg and reaching maximum doses of 2.0 mg) of risperidone for 6 weeks. During that period, they were evaluated weekly for side effects and for clinical and neuropsychological effects of treatment. After 6 weeks, most clinical and neuropsychological tests were repeated. We reported on the effects of treatment in our first 4 cases[71] and have since completed a fifth case. All subjects thus far showed marked improvements in a demanding test of auditory attention, and all subjects showed reduced negative symptoms after 6 weeks. In 3 cases, reductions in negative symptoms were marked; in 2 they were modest. Side effects, when they occurred, were mild to moderate in severity. No one requested the discontinuation of treatment, but in some cases the doses were lowered to reduce discomfort.

Future directions

Our initial application of the schizotaxia treatment protocol is encouraging, as all 5 cases showed reductions in negative symptoms and neuropsychological deficits. We stress the preliminary nature of these findings, however, and do not yet recommend the use of risperidone or other medications to treat schizotaxia. Larger, controlled studies are needed to determine if the treatment implications of these pilot findings are correct.

Despite this caveat, however, our findings suggest the feasibility of developing treatment strategies for adult schizotaxia. It is clear that we are only starting this process. Perhaps the most important tasks for the near future, in addition to the need for more methodologically rigorous replications, is the validation of schizotaxia as a syndrome. In order to accomplish this task, it will be useful to change our conceptualization of schizophrenia somewhat from the historical view of a discrete, categorical entity whose diagnosis depends on the clinical symptoms of psychosis. Instead, a more fruitful approach may be to incorporate a dimensional, neurodevelopmental perspective in schizophrenia that includes neurobiological and neuropsychological measures occurring prior to the development of psychosis (schizotaxia). At some point, molecular biological data will also be included in this conception, as the genes that cause schizotaxia are located. As the validity of schizotaxia becomes established, the risk (for subsequent psychosis) provided by its component features will become measurable. That knowledge base will provide the foundation for strategies aimed at the prevention of schizophrenia, perhaps in the not-too-distant future. ❑

Basic research

Conceptualizaciones respecto al riesgo de padecer esquizofrenia: sus implicancias clínicas

Históricamente, los criterios diagnósticos del Diagnostic and Statistical Manual of Mental Disorders *(DSM) para esquizofrenia han enfatizado algunas características que incluyen: síntomas de psicosis, una disociación de síntomas de su etiología, una dependencia de los síntomas clínicos y una aproximación categorial para clasificar el trastorno. Aunque este enfoque resulta bastante útil, también tiene sus limitaciones. En este artículo se revisan estas limitaciones y se señala la importancia de incorporar datos recientes, provenientes de investigaciones acerca de los aspectos genético-biológicos y del neurodesarrollo de la esquizofrenia, en las concepciones actuales de este trastorno. También se revisa el concepto de "esquizotaxia", que engloba este punto de vista; aparece antes del comienzo de la psicosis e hipotéticamente representaría la vulnerabilidad a la esquizofrenia. Si esta hipótesis en este punto es correcta, significa que la identificación de individuos con esquizotaxia eventualmente facilitaría el desarrollo de estrategias de prevención al reconocer una condición premórbida (pero clínicamente significativa) para la esquizofrenia. Sin embargo, la identificación de componentes biológicos o neuropsicológicos de la esquizotaxia facilitaría bases más específicas para el desarrollo de nuevas intervenciones terapéuticas. Nuestros intentos iniciales para desarrollar protocolos para la evaluación y tratamiento de la esquizotaxia son alentadores y se revisan en este artículo.*

Conceptualisation d'une prédisposition à la schizophrénie : implications cliniques

Traditionnellement, les critères diagnostiques du Diagnostic and Statistical Manual of Mental Disorders *(DSM) pour la schizophrénie ont mis l'accent sur différents aspects, notamment les symptômes psychotiques; l'indépendance entre symptômes et étiologie; la place prépondérante de la clinique et une approche catégorielle pour classer ce trouble. Cependant, bien que les caractéristiques ainsi définies aient leur utilité, elles ont aussi des limites. Le présent article passe ces dernières en revue, et souligne l'importance d'intégrer dans les conceptions actuelles de la schizophrénie les données récentes sur les origines génétiques/biologiques et neurodéveloppementales de cette maladie. Cet article fait également le point sur le concept de "schizotaxie", qui survient avant l'apparition de la psychose, et constituerait une prédisposition à la schizophrénie. Si notre hypothèse concernant ce point s'avère exacte, l'identification des personnes schizotaxiques pourrait faciliter le développement de stratégies préventives en déterminant un état prémorbide (mais cliniquement significatif) de la schizophrénie. De plus, l'identification des composantes biologiques et neuropsychologiques de la schizotaxie devrait fournir des bases plus spécifiques pour le développement de nouveaux traitements. Nos premières tentatives de mise en place de protocoles pour l'évaluation et le traitement de la schizotaxie, décrites ici, paraissent d'ores et déjà encourageantes.*

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