Clinical research

Schizophrenia: vulnerability versus disease

Ming T. Tsuang, MD, PhD, DSc, FRCPsych;
William S. Stone, PhD; Stephen V. Faraone, PhD

One of the most important trends in the treatment of schizophrenia involves its early diagnosis and intervention. The ultimate goal of research is the prevention of the disorder. A major impediment to the development of prevention strategies, however, is that we do not yet know what the liability for schizophrenia is before the onset of psychosis. Consequently, early treatment attempts are focused on the "prodrome," which involves the early symptoms of psychosis. In a companion paper, we recently suggested that prevention work should focus not only on the prodrome, but also on "schizotaxia," which is a clinically meaningful condition that may reflect the vulnerability to schizophrenia in the absence of psychosis. Because schizotaxia can be assessed prior to the prodrome, studies of schizotaxia might lead to more effective prevention programs. We continue the characterization of schizotaxia in this paper by focusing on the etiological roots of schizotaxia, plus its likely neurodevelopmental course, clinical expression, and treatment. Finally, the importance of including neurobiological variables in the conceptualization and eventual diagnosis of schizotaxia is reviewed.

An understanding of how schizophrenia develops is essential for developing treatment strategies aimed at preventing the disorder. Before such strategies can be formulated, it will be necessary to identify the liability for schizophrenia. That is, what is the vulnerability to schizophrenia before the onset of psychosis? Recently, we addressed this issue in a companion paper to this one by describing "schizotaxia," a clinically meaningful condition that may reflect liability for schizophrenia.[1] In this paper, we describe the model of schizotaxia further by focusing on its etiology and development, and on its clinical, neuropsychological, and biological bases. We begin with a brief review of the concept, followed by a consideration of its genetic and environmental etiologies, and its likely neurodevelopmental course. Associated clinical and neuropsychological components of schizotaxia are then reviewed, followed by an update on our attempts to use these symptoms to develop treatment protocols. Finally, prospects for future research center on the need to incorporate biological function into the conceptualization and treatment of the syndrome.

Schizotaxia

Paul Meehl introduced the term "schizotaxia" in 1962 to describe the genetic predisposition to schizophrenia,[2] which he believed resulted in a subtle, neural integrative defect. He proposed that schizotaxic individuals would eventually develop either schizotypy or schizophrenia, depending on environmental circumstances. Although schizotypy (in the form of schizotypal personality disorder) eventually entered the psychiatric nomenclature, schizotaxia did not. Instead, it became associated with

Author affiliations: Harvard Medical School Department of Psychiatry at the Massachusetts Mental Health Center; Brockton West Roxbury Veterans Affairs Medical Center; Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, Mass, USA (Ming T. Tsuang, William S. Stone, Stephen V. Faraone); Department of Epidemiology, Harvard School of Public Health, Boston, Mass, USA (Ming T. Tsuang); Pediatric Psychopharmacology Unit, Psychiatry Service, Massachusetts General Hospital, Boston, Mass, USA (Stephen V. Faraone)

Address for correspondence: Ming T. Tsuang, MD, PhD, Stanley Cobb Professor of Psychiatry, and Head, Harvard Medical School Department of Psychiatry at the Massachusetts Mental Health Center, 74 Fenwood Rd, Boston, MA 02115, USA (e-mail: ming_tsuang@hms.harvard.edu)

the premorbid, neurobiological substrate of schizophrenia, but not with a clinically meaningful syndrome.

Now, after more than three decades of research, the accumulated evidence suggests that schizotaxia is, in fact, a clinically consequential condition *and* a risk factor or marker for subsequent psychosis. As such, it encompasses aspects of both vulnerability and disease. In our reformulation of the concept, differences emerged from Meehl's original view. While our use of the term remains consistent with Meehl's view of it as the underlying defect among people genetically predisposed to schizophrenia, it differs from his theory in at least four significant ways. First, unlike Meehl, we view the etiology of schizotaxia as genetic and environmental, instead of only genetic. Second, we believe the genetic etiology of schizotaxia is best explained by a multifactorial, polygenic model, rather than by a single, major gene (Meehl promulgated his theory before molecular genetic data were available, which may partly account for this aspect of his theory). Third, we do not view schizotypy or schizophrenia as the only, or even the most common, outcomes of schizotaxia, while Meehl viewed them as the primary end points (even after a later modification of his views).[3] Fourth, unlike Meehl, we have begun to identify the components of schizotaxia and to operationalize the concept. Each of these points will be considered in the course of the following sections, starting with a consideration of the origins of the disorder.

The etiology of schizophrenic illness

Genetic origins

The familial nature of schizophrenia is well known.[4] In a review of 40 European studies selected for similarities in diagnostic and ascertainment procedures, Gottesman showed the following approximate lifetime risks for schizophrenia to relatives of schizophrenic patients: parents, 6.0%; siblings, 9.0%; offspring (of one parent with schizophrenia), 13.0%; and offspring of two schizophrenic parents, 46.0%. Risks to second-degree relatives ranged from 6.0% for half-siblings to 2.0% for uncles and aunts, while the risk for first cousins, a type of third-degree relative, was approximately 2.0%. Modern family studies, using narrower diagnostic criteria than those employed in earlier European studies, have essentially confirmed both the pattern of risk in families, and the approximate rates at which they occur.[5]

Familial risk rates, of course, do not necessarily imply genetic causation. Consistent with genetic hypotheses, however, higher risk rates among relatives are associated with greater degrees of biological relatedness to a schizophrenic patient. Moreover, behavioral genetic designs, including the use of twin and adoption studies, provide overwhelming evidence of a large genetic component in most cases.[4,5] For example, adoption studies show that the biological offspring of patients with schizophrenia show elevated risks for schizophrenia, even when they are adopted away at birth and raised by nonschizophrenic parents.[6] Twin studies also show that concordance rates for schizophrenia are higher in identical twins (who share 100% of their genes) than they are in fraternal twins (who share an average of 50% of their genes). Estimates of the heritability of schizophrenia vary depending on the methods of ascertainment. Kendler and Diehl[7] reported an average heritability of around 70% in a series of twin studies, while recent studies using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), DSM-III-R,* or *DSM-IV* diagnostic criteria demonstrated heritability estimates between 80% to 86%.[8-10] It should be stressed that, while these heritability estimates are quite substantial, they are influenced by a variety of factors, including the nature of the sample (eg, its size), the phenotypic criteria used for diagnosis, the statistical model used, the effect sizes of relevant variables, and environmental factors.

Findings from behavioral genetic studies are of particular importance to the present discussion because they provide evidence that schizophrenia genes predispose their carriers not only to schizophrenia, but also to schizophrenia-like disorders, such as schizoaffective disorder and schizotypal personality disorder. These conditions are less severe than schizophrenia, but may be caused by the same genes,[4] suggesting a spectrum of liability for schizophrenic illness. Consistent with this view, we proposed that genes involved in conferring liability for schizophrenia are a major etiological component of schizotaxia.[11] Moreover, schizotaxia may be a "truer" expression of the genes that predispose to schizophrenic illness than is the diagnostic entity of schizophrenia itself, because the latter condition may include less (etiologically) specific effects of psychosis.[1,12]

Environmental origins

Despite the overwhelming evidence of a genetic influence in schizophrenia, it is clear that the presence of genes that

confer liability for schizophrenia is not sufficient to cause the disorder in most cases. The case for environmental influence in schizophrenia/schizotaxia incorporates evidence from several sources. First, the same behavioral genetic studies that show the importance of genetic factors in schizophrenic illness also underscore the importance of environmental variables. For example, in family studies, no degree of biological relatedness, including the circumstance of having two schizophrenic parents, results in the development of schizophrenia 100% of the time. As described above, the liability in that case only approaches an average of 50%. Similarly, the risk of developing schizophrenia in a monozygotic (MZ) cotwin (who shares 100% of the other twin's genes) whose sibling develops schizophrenia is also about 50%, which is far lower than would be predicted if genetic influence were the only etiologic factor. Consistent with such findings, Gottesman and Bertelsen[13] showed that rates of schizophrenia in the offspring of identical twins who were discordant for schizophrenia were equal. In all these examples, individuals who possessed the schizophrenia genotype did not necessarily express the disorder. Even the high estimates of heritability described above must be considered in context. Those studies showed that about 70% to 85% of the differences between people who develop schizophrenia and those who do not may be attributed to genetic factors (in the particular samples that were studied). They did not mean that the overall influence of genetic factors is that high.

Environmental influences encompass a variety of dimensions. They may be shared by individuals in the same household (whether related or not) or unshared (that is, unique, even for MZ twins), and they may occur at any point in development, from the moment of conception through prenatal development, birth, maturation, and senescence. The differential impact of environmental variables often varies as a function of the stage of development at which they are introduced. Environmental components include psychosocial, biological, and physical factors that could cause even MZ twins, with their common genetic endowments, to experience their worlds quite differently. For example, they may experience different levels of prenatal and perinatal factors, such as the adequacy of their blood supplies, their positions in the womb, and birth complications. Later, they may experience different home and school environments, and different marital experiences, occupational events, or surroundings.[14,15] These differences are probably meaningful, as nonshared environmental influences account for almost all of the variance in liability to schizophrenia attributable to environmental effects in several recent twin studies.[6,8,16]

This discussion thus emphasizes the importance of environmental variables in addition to genetic ones. How do the two types of variables interact to cause schizophrenia? There is substantial evidence that, in most cases, schizophrenia is caused by a multifactorial process consisting of multiple genes that act in combination with adverse environmental factors.[4,17,18] Although the number of schizophrenia genes is unknown, there is a broad consensus that single gene theories of schizophrenia are not viable, even if such theories allow for multiple single gene variants.[19-22] The multifactorial model of schizophrenia has some support from segregation analysis studies,[23,24] and cannot be discounted as a viable model of the etiology of schizophrenia.

Within the domain of multifactorial models, both additive genetic and interactive models have been posited.[25] Certainly, genes and environments always interact, but the point deserves emphasis because it suggests that environmental factors may have differential effects on individuals with different genotypes. In this view, genetically mediated factors underlie differences in sensitivity to environmental factors, and/or from environmentally mediated genetic effects. The consideration of genetic-environmental influences may help better understand the nature of at least some environmental risk factors. Just as geneticists search the entire genome for all of the many genes that affect susceptibility to schizophrenia, so must environmental researchers search the entire "envirome" for all environmental risk factors that affect the disorder. Once we understand the sum and interaction of all effects from the genome and from the envirome, we will have solved the puzzle of schizophrenia.

To date, at least two broad features of the envirome are candidate risk factors for schizophrenia: psychosocial factors and pregnancy/delivery complications. Evidence from several adoption studies attest to the importance of psychosocial factors.[5] For example, Wahlberg et al,[26] using data from the Finnish adoption studies, showed that schizophrenic thought disorder in young adult offspring of schizophrenic mothers was more likely when their adoptive mothers showed deviant communication patterns.

The influence of pregnancy and delivery complications occurs earlier in development than does the psychosocial factor mentioned above. As such, it may have a greater impact on the development of schizotaxia, and will be dis-

cussed further. More generally, the study of developmental abnormalities, like pregnancy and delivery complications, and their interactions with genetic risk factors, facilitates an understanding of precursor states for schizophrenia.[27] Retrospective studies show, for example, that a history of labor and delivery complications are more common in individuals who later develop schizophrenia, compared with normal controls.[28-31] One of these is preeclampsia, which results in both fetal hypoxia and a ninefold increase in the risk for subsequent schizophrenia.[32] In reviewing data from the Philadelphia cohort of the National Collaborative Perinatal Project (NCPP), Cannon[33] noted a dose-dependent relationship between risk for schizophrenia and severity of perinatal hypoxia, and between the risk for schizophrenia and the number of hypoxia-related birth complications among children of schizophrenic parents. Pregnancy and delivery complications that were not related to hypoxia did not increase the subsequent risk for schizophrenia among children of schizophrenic patients.

The importance of specifying which type of obstetric complication is associated with risk for subsequent schizophrenia was underscored recently by several researchers (see, for example, references 34 and 35), who noted that grouping them together produced a somewhat inconsistent body of literature. Other specific obstetric risk factors were reported to increase the risk for schizophrenia include multiparity, maternal bleeding during pregnancy, winter births, malnutrition, and extreme prematurity.[36,37] Moreover, viral infections during pregnancy have been related to a predisposition for adult schizophrenia.[38] Although the literature on the effects of viruses requires more clarification, there are many reports of positive relationships between such infections and the later development of schizophrenia.[31] Interestingly, some viral infections associated with schizophrenia occurred in the second trimester (see, for example, reference 39) and may help explain postmortem findings of brain anomalies related to that stage of development (see, for example, reference 40). Other studies, however, suggested that viral infections throughout pregnancy and the neonatal period elevated the risk for subsequent schizophrenia.[41]

Environmental factors thus appear to act in concert with genetic factors to produce schizotaxia—the liability for schizophrenia. At least two conclusions relevant for the formulation of schizotaxia may be drawn from this discussion. First, it is clear that both genetic and environmental etiological factors have biological consequences early in development. For this reason, and because these consequences cannot be parsed out into their purely genetic and purely environmental components, we have reformulated Meehl's view that schizotaxia represents only the genetic predisposition to schizophrenia. In our view, schizotaxia results from a combination of both genetic and environmental etiologies. Because it may result from the effects of multiple genes and multiple environmental factors, it may be a heterogeneous condition, both clinically and etiologically.

Second, the action of these etiological factors in early development suggests the likelihood that schizotaxia is a neurodevelopmental condition. *Figure 1* reflects our view of schizotaxia as the liability for schizophrenia. The top of the figure illustrates our premise that schizotaxia results from a combination of genetic and adverse environmental events. Consistent with the view that schizotaxia is a
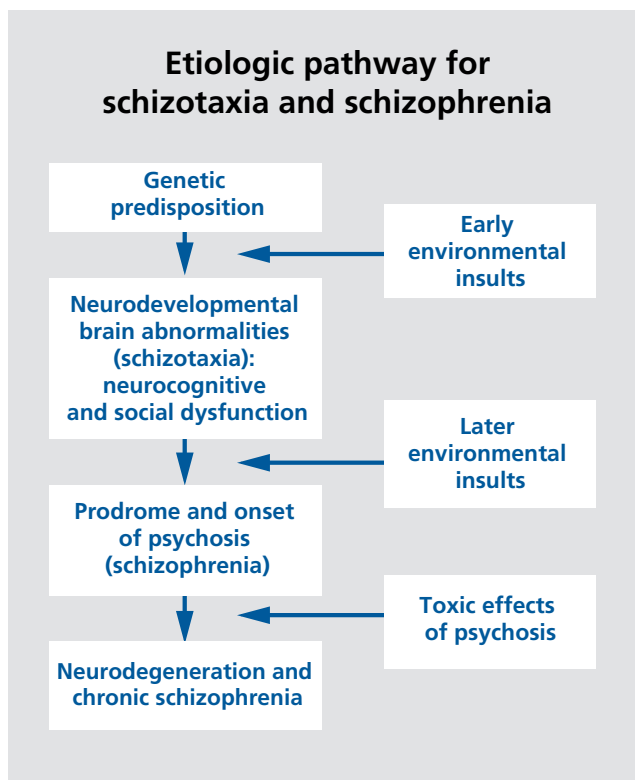

Etiologic pathway for schizotaxia and schizophrenia

Figure 1. Model of the neurodevelopmental course of schizotaxia. See text for details.
Reproduced from reference 42: Tsuang MT. Defining alternative phenotypes for genetic studies: what can we learn from studies of schizophrenia. *Neuropsychiatric Genet.* 2000. In press. Copyright © 2000, Wiley-Liss, Inc.

neurodevelopmental disorder, it is likely to involve neurobiological abnormalities, as well as clinical and neuropsychological difficulties. The middle of the figure reflects the premise that later environmental events (eg, adverse psychosocial events, substance abuse, head injury) interact with schizotaxia to produce prodromal symptoms, and then schizophrenia. These events stress the inability of vulnerable individuals to compensate—either behaviorally or neurobiologically—to additional challenges, sources of stress, or, possibly, to continued maldevelopment of prefrontal areas in the second and third decades of life. The bottom portion of the figure shows that psychosis has "toxic" effects of its own, which result in chronic schizophrenia and, possibly, neurodegeneration. Note that in this model, psychosis is a condition that is distinct from the predisposition to schizophrenia. As noted above, schizotaxia would thus reflect a truer expression of schizophrenia genes than would schizotaxia plus psychosis (ie, schizophrenia).

Clinical features and treatment of schizotaxia

In light of the etiological and neurodevelopmental framework discussed above, what does the schizotaxia phenotype look like? Comprehensive review of many schizotaxic features have already been published (see, for example, the issue of the *Schizophrenia Bulletin* edited by Moldin and Erlenmeyer-Kimling,[43] and also reference 11). Here we seek to summarize portions of that information that have been relatively well studied and that will facilitate the development of strategies aimed at treating schizotaxia and (eventually) preventing schizophrenia. Two dimensions likely to meet these criteria, negative symptoms and neuropsychological deficits, will be emphasized, followed by a summary of our initial attempts to employ these dimensions to create operational criteria for a treatment protocol. We will then briefly consider neurobiological aspects of schizotaxia, in the context of further understanding and treating the condition.

Negative symptoms

Family, twin, and adoption studies provide firm evidence that relatives of patients with schizophrenia are at high risk for schizotypal personality disorder,[44-46] which leads to the issue of which schizotypal symptoms are most common. Gunderson et al,[47] for example, showed that such

relatives were at high risk for social isolation, interpersonal dysfunction, and impoverished affective experiences. In that study, mild psychotic-like symptoms, such as recurrent illusions and magical thinking, were more common in relatives who were diagnosed with borderline personality disorder. Tsuang et al[48] reported that negative symptoms (especially flat affect and avolition) were significantly elevated in the families with schizophrenia, while positive symptoms were not. In the Roscommon family study, odd speech, social dysfunction, and negative symptoms strongly discriminated relatives of schizophrenic patients from controls, while positive symptoms, suspicious behavior, and avoidant symptoms were less discriminating.[49]

Consistent with these studies, psychometric assessments of schizotypal symptoms among relatives of patients with schizophrenia show a predominance of negative rather than positive symptoms (see, for example, reference 50). In summary, the literature thus far shows that nonpsychotic relatives in families with schizophrenia are more likely to express negative symptoms than positive symptoms, although, as the Roscommon study showed, positive schizotypal symptoms do occur in this group.

Neuropsychological deficits

Compared with normal control subjects, nonpsychotic relatives of schizophrenic patients show deficits in a variety of cognitive domains.[11,51,52] Domains that show the most consistent deficits include auditory attention, verbal memory, and executive function (eg, abstraction).[11,52] A recent examination of first-degree, nonpsychotic relatives who had been evaluated 4 years previously[52,53] showed that their neuropsychological deficits were stable over time.[54] Additional analyses showed significant intercorrelations among the three functions within the relatives, but not among a group of controls, who mainly showed significant correlations within different tests of the same function.[55] The significant correlations among relatives between attention and verbal memory and between attention and abstraction differed significantly from these correlations in the control group. Thus, neuropsychological functions that are putative risk indicators for schizophrenia co-occur to a greater degree within relatives than they do within controls. The finding that other neuropsychological functions did not co-occur to a greater degree within relatives provides further support for the risk indicator status of attention, verbal memory, and abstraction.

Clinical research

These studies and others suggest that neuropsychological impairments in relatives of schizophrenic patients are stable traits caused by the set of genes that also increases the predisposition to schizophrenia.[53-58] Interestingly, when our sample of relatives was divided into simplex (ie, one schizophrenic relative) and multiplex (two schizophrenic relatives) groups, the multiplex sample performed more poorly in several domains, including estimated intelligence, immediate and delayed verbal memory, and immediate visual, nonverbal memory.[59] This finding is particularly consistent with the multifactorial model of schizophrenia,[4,17,18] which hypothesizes that no one gene or environmental factor causes schizophrenia. Rather, it is the sum of multiple genes and environmental factors that crosses some threshold value and leads to the disorder. If this is true, then a graded genetic predisposition to the disorder must exist, such that the probability of developing schizophrenia or another schizophrenia spectrum disorder (or showing related neuropsychological impairments) increases as the degree of liability increases. Presumably, multiplex families harbor more schizophrenia genes than simplex families. Thus, our finding of greater impairments in relatives in multiplex families is consistent with the predictions of a multifactorial model.

The emphasis accorded to negative symptoms and neuropsychological deficits may evolve as other components (eg, psychosocial and neurobiological factors) are integrated into the model. It is significant, however, that in our samples these core features of schizotaxia (negative symptoms and neuropsychological impairments) occur in 20% to 50% of first-degree relatives of patients with schizophrenia.[52,53] In contrast, less than 10% of adult family members of schizophrenic patients will be diagnosed with schizotypal personality disorder, which means that, unlike schizotypal personality, schizotaxia appears to be common among relatives of schizophrenic patients. Because schizotypal personality should be evident by adulthood, the finding that many schizotaxic adults are not schizotypal shows that the former condition does not always evolve into the latter. Moreover, only about 10% of first-degree relatives will develop schizophrenia,[4] emphasizing further that schizotaxia may be a relatively stable condition for many adult relatives of schizophrenic patients. This point does not obviate the more immediate challenge of validating schizotaxia as a syndrome, and distinguishing it clearly from schizotypal personality disorder. One way to achieve the latter goal might be to designate schizotaxia as the syndrome of negative symptoms and neuropsychological dysfunction observed among relatives of schizophrenic patients, and schizotypal personality disorder as the schizophrenia-like syndrome in which positive symptoms dominate the clinical picture. Reformulating the diagnoses in this manner would increase the homogeneity of schizotypal personality and allow researchers to define schizotaxia in a manner that might further validate its status as a syndrome.

Treatment of schizotaxia

There are at least two reasons to consider treating schizotaxia. First, because schizotaxia may be a more specific expression of schizophrenia genes than is the clinical diagnosis of schizophrenia, the treatment of schizotaxia might prevent or attenuate the clinical, social, and pathophysiological difficulties associated with psychosis. Second, the treatment of schizotaxia in nonpsychotic relatives could result in the attenuation of clinically meaningful symptoms. A variety of psychotherapeutic approaches might be appropriate for this population, as might some pharmacological approaches.[11] We proposed this latter course of action in a pilot series of four relatives with schizotaxia.[60] Since that paper was published, we have completed two additional cases. The full inclusion and exclusion criteria were described in that report and in the companion article to this paper in *Dialogues in Clinical Neuroscience*.[1] The clinical criteria for schizotaxia included moderate deficits in at least two of the following three neuropsychological domains: long-term verbal memory, attention, and executive functions. Moderate deficits were defined as at least 2 standard deviations below normal in one neuropsychological domain, and at least 1 standard deviation below normal in a second neuropsychological domain; moderate levels of negative symptoms were defined as 6 or more scores on the Schedule for the Assessment of Negative Symptoms rated 3 or higher. Individuals who met these criteria and who provided informed consent received low doses of risperidone (0.25-2.0 mg) for 6 weeks. Side effects were temporary and mainly mild. Five out of six individuals showed marked improvements in attention, and mild-to-moderate reductions in negative symptoms. The sixth subject did not show improvement in either area. This subject also differed from the other cases in other ways, as her level of overall cognitive ability was below normal (estimated IQ=75), raising the possibility

that treatments might be less effective when the ability to utilize them falls below certain levels. Regardless of why the 6th case did not improve, however, the cognitive and clinical improvements in 5 out of 6 individuals is encouraging. We stress that these results are preliminary, and do not advocate the use of this treatment clinically, until larger, better-controlled trials determine the reliability and validity of our findings.

Current challenges

What must be accomplished to further the study of schizotaxia and facilitate the development of prevention strategies for schizophrenia? Perhaps most importantly, schizotaxia needs to be validated as a syndrome.[12] Closely related to this goal is the need to understand the concomitant dimensions of the condition. Among the more important of these are its underlying biological substrates, since they are likely to represent the effects of schizophrenia genes more closely than are clinical symptoms. Eventually, the inclusion of biological criteria is likely to improve the specificity of diagnostic criteria, both for schizotaxia and for schizophrenia.

In the near future, the study of biological measures can further an understanding of schizotaxia in at least three interacting ways. First, it can help define and validate the syndrome. There is a large body of literature showing neurobiological abnormalities in schizophrenia, at many levels of analysis. These range from relatively macroscopic changes in brain morphology, such as enlarged ventricles, to molecular biological abnormalities, such as reduced transcription of messenger RNAs for various proteins in circumscribed brain regions. A smaller but substantial subset of these abnormalities also occurs in family members and, like negative symptoms and neuropsychological deficits, may provide phenotypes for schizotaxia. Reductions in ventricular size[61] or in brain regions, such as the amygdala, hippocampus, and thalamus,[62,63] diminished sensory gating of auditory P50 evoked potentials (see, for example, references 64 and 65), lowered levels of plasma homovanillic acid,[66] and reductions in hippocampal *N*-acetyl aspartate (NAA)[67] are among a growing list of abnormalities that are currently generating research. Which, if any, of these abnormalities are related to the features of schizotaxia that were outlined above? One way to validate schizotaxia will be to determine whether current schizotaxic features (ie, negative symptoms and neuropsychological

deficits) are associated with these or other biological abnormalities. As these associations are made, the biological abnormalities may come to be incorporated into the conception of schizotaxia and, presumably, into the diagnostic criteria for the syndrome.

The second way that biological features can facilitate the conceptualization of schizotaxia is by helping to differentiate features of schizotaxia that are primarily markers, or consequences, of the disorder from those that are more important in producing the symptoms of the disorder. This is certainly a complicated issue at this stage in our understanding of schizotaxia, and it would probably be premature to classify any biological abnormality in relatives as etiologically insignificant. However, some types of abnormalities may be particularly informative, and more clearly relevant to schizotaxic symptoms. Among these, for example, are deficits involving hippocampal circuitry that is involved in mediating the experience-dependent synaptic plasticity that underlies some forms of learning and memory. Hippocampal deficits are also significant in schizophrenia because they may contribute to dorsolateral prefrontal dysfunction, and to psychotic symptoms (see, for example, references 40, 65, and 68). In schizophrenic patients, these deficits may include smaller cell sizes and neuropils, and reduced transcription of certain proteins involved in neuronal transmission, such as growth-associated protein–43 (GAP-43) and subunits of non–*N*-methyl-D-aspartate (NMDA) glutamate receptors.[68] These latter deficits involve the "trisynaptic circuit" of the hippocampus, including the CA3 region of Ammon's horn, which is also a locus of impaired sensory gating.[65] The conceptual (eg, its putative roles in learning and memory, and in filtering out, or gating, unimportant information from the environment) and empirical (ie, its demonstrated abnormalities in schizophrenic patients and their relatives) significance of the hippocampus thus underscores the importance of determining whether hippocampal-based deficits are associated with the clinical and neuropsychological symptoms of schizotaxia we described above. Similar arguments may be made for other brain regions.

The third and most important reason for studying the neurobiological etiology of schizotaxia is to provide a foundation for the rational development of treatment strategies for schizotaxia, and prevention strategies for schizophrenia. Our initial treatment of schizotaxia (described above) involved low doses of risperidone,

one of the newer antipsychotic medications, because we reasoned that it might ameliorate some of the same problems in schizotaxic relatives that it does in schizophrenic patients. While the reasons for its effectiveness remain unclear, they probably do not include its antipsychotic properties, since the schizotaxic relatives were (by definition) not psychotic. As neurobiological mechanisms of schizotaxia become elucidated, treatments will likely include options that are broader and more specific than antipsychotic treatments alone. Some of these may be tested in the near future. For example, the demonstration that nicotine transiently normalizes impaired sensory gating in relatives implicates cholinergic neurotransmission in the normal mediation of the "filtering" function.[69] Interestingly, we recently found that glucose, which also facilitates hippocampal cholinergic function (see, for example, references 70 and 71), improves long-term verbal memory in schizophrenic patients treated with clozapine.[72] Whether glucose can also attenuate cognitive dysfunctions in schizotaxia remains to be tested, but it does illustrate the possibility that a broad range of nonanti-psychotic treatments (with or without concomitant low doses of antipsychotic medications) may be useful in treating schizotaxia.

As the biological bases of schizotaxia become clearer, so will diagnostic criteria for the syndrome. This will allow the development of more targeted treatment strategies and homogeneous samples of research subjects. If successful treatments for schizotaxia can be demonstrated in adults, then the most important goal of schizotaxia research can be embarked upon, which is the prevention of schizophrenia. While we are certainly not at that point yet, we may be cautiously optimistic that the issue now is more related to when, rather than if, we will achieve that goal. ❏

REFERENCES

1. Tsuang MT, Stone WS, Faraone SV. Conceptualization of the liability for schizophrenia: clinical implications. *Dialogues Clin Neurosci.* 1999;1:153-164.
2. Meehl PE. Schizotaxia, schizotypy, schizophrenia. *Am Psychol.* 1962;17:827-838.
3. Meehl PE. Schizotaxia revisited. *Arch Gen Psychiatry.* 1989;46:935-944.
4. Gottesman II. *Schizophrenia Genesis: The Origin of Madness.* New York, NY: Freeman; 1991.
5. Tsuang MT, Stone WS, Faraone SV. Schizophrenia: a review of genetic studies. *Harv Rev Psychiatry.* 1999;7:185-207.
6. Kety SS, Wender PH, Jacobsen B, et al. Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen study in the rest of Denmark. *Arch Gen Psychiatry.* 1994;51:442-455.
7. Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophr Bull.* 1993;19:261-285.
8. Cannon T, Kaprio J, Lonnqvist J, Huttunen M, Koskenvuo M. The genetic epidemiology of schizophrenia in a Finnish twin cohort. *Arch Gen Psychiatry.* 1998;55:67-74.
9. Farmer AE, McGuffin P, Gottesman II. Twin concordance for DSM-III schizophrenia: scrutinizing the validity of the definition. *Arch Gen Psychiatry.* 1987;44:634-641.
10. Onstad S, Skre I, Torgersen S, Kringlen E. Twin concordance for DSM-III-R schizophrenia. *Acta Psychiatr Scand.* 1991;83:395-401.
11. Faraone SV, Green AI, Seidman LJ, Tsuang MT. "Schizotaxia": clinical Implications and new directions for research. *Schizophr Bull.* In press.
12. Tsuang MT, Stone WS, Faraone SV. Towards reformulating the diagnosis of schizophrenia. *Am J Psychiatry.* 2000;157:1041-1050.
13. Gottesman II, Bertelsen A. Confirming unexpressed genotypes for schizophrenia. Risks in the offspring of Fischer's Danish identical and fraternal discordant twins. *Arch Gen Psychiatry.* 1989;46:867-872.
14. Pike A, Plomin R. Importance of nonshared environmental factors for childhood and adolescent psychopathology. *J Am Acad Child Adolesc Psychiatry.* 1996;35:560-570.
15. Reiss D, Plomin R, Hetherington EM. Genetics and psychiatry: an unheralded window on the environment. *Am J Psychiatry.* 1991;148:283-291.
16. Kendler KS, Gruenberg AM, Kinney DK. Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish adoption study of schizophrenia. *Arch Gen Psychiatry.* 1994;51:456-468.
17. Tsuang MT, Faraone SV. Epidemiology and Behavioral Genetics of Schizophrenia. In: Watson SJ, ed. *Biology of Schizophrenia and Affective Disease.* New York, NY: Raven Press; 1994:163-195.
18. Gottesman, II, McGuffin P, Farmer AE. Clinical genetics as clues to the "real" genetics of schizophrenia (a decade of modest gains while playing for time). *Schizophr Bull.* 1987;13:23-47.
19. Gottesman II, McGue M. Mixed and mixed-up models for the transmission of schizophrenia. In: Cichetti D, Grove WM, eds. *Thinking Clearly About Psychology: Essays in Honor of Paul E. Meehl.* Minneaplois, Minn: University of Minnesota Press; 1990.
20. Gottesman II, Carey G, Hanson DR. Pearls and perils in epigenetic psychopathology. In: Guze SB, Earls FJ, Barrett JE, eds. *American Psychopathological Association Series. Childhood Psychopathology and Development.* New York, NY: Raven Press; 1983:287-300.
21. McGue M, Gottesman II, Rao DC. The transmission of schizophrenia under a multifactorial threshold model. *Am J Hum Genet.* 1983;35:1161-1178.
22. McGuffin P, Farmer A, Gottesman II. Is there really a split in schizophrenia? The genetic evidence. *Br J Psychiatry.* 1987;150:581-592.
23. Faraone SV, Lyons MJ, Tsuang MT. Schizophrenia: mathematical models of genetic transmission. In: Tsuang MT, Simpson JC, eds. *Nosology, Epidemiology and Genetics.* Vol 3. Amsterdam, The Netherlands: Elsevier Science Publishers BV; 1988:501-530.

Esquizofrenia: vulnerabilidad versus enfermedad

Uno de los aspectos más importantes en el tratamiento de la esquizofrenia es el diagnóstico y la intervención precoces. El objetivo último de la investigación en esta enfermedad es su prevención. Uno de los impedimentos al desarrollo de estrategias de prevención, sin embargo, es el hecho que aun no conocemos cuál es la probabilidad para desarrollar esquizofrenia previo a la aparición de la psicosis. En consecuencia, los intentos de tratamiento precoz se focalizan en el "pródromo", el cual involucra síntomas precoces de psicosis. En un artículo complementario, nosotros sugerimos recientemente que el trabajo de prevención no debe centrarse sólo en el pródromo, sino también en la "esquizotaxia", que es una condición clínicamente significativa que puede reflejar la vulnerabilidad a la esquizofrenia en ausencia de psicosis. Ya que la esquizotaxia puede ser evaluada previo al pródromo, los estudios de esquizotaxia pueden conducir a programas de prevención más efectivos. En este artículo nosotros continuamos con la caracterización de la esquizotaxia al referirnos a las raíces etiológicas de ella, como también a su probable curso durante el neurodesarrollo, su expresión clínica y su tratamiento. Finalmente se revisa la importancia de incluir variables neurobiológicas en la conceptualización y eventual diagnóstico de esquizotaxia.

Schizophrénie : vulnérabilité versus maladie

L'importance d'un diagnostic et d'une prise en charge précoces du traitement de la schizophrénie est actuellement de plus en plus reconnue. L'objectif ultime d'une telle recherche est la prévention de la maladie. Néanmoins, l'obstacle majeur au développement de stratégies préventives est que nous ne sommes pas encore capables de définir la susceptibilité d'un patient vis-à-vis de la schizophrénie avant la survenue de la psychose. De ce fait, des tentatives de traitement précoce sont centrées sur les " prodromes ", qui comprennent les symptômes précoces de la psychose. Dans un article précédent traitant du même thème nous avons récemment suggéré que le travail de prévention devait se concentrer non seulement sur les prodromes mais également sur la " schizotaxie ", qui représente un état cliniquement significatif qui pourrait refléter la vulnérabilité vis-à-vis de la schizophrénie en l'absence de psychose. Puisque la schizotaxie peut être évaluée avant la survenue des prodromes, les études sur la schizotaxie pourraient conduire à des programmes de prévention plus efficaces. Dans cet article nous poursuivons la caractérisation de la schizotaxie en nous intéressant tout particulièrement à ses bases étiologiques, ainsi qu'à sa probable évolution neuro-développementale, son expression clinique et son traitement. Enfin, l'importance de l'inclusion des variables neurobiologiques dans la conceptualisation et le diagnostic éventuel de la schizotaxie est passée en revue.

24. Faraone SV, Tsuang MT. Quantitative models of the genetic transmission of schizophrenia. *Psychol Bull.* 1985;98:41-66.

25. Kendler KS. Genetic epidemiology in psychiatry: taking both genes and environment seriously. *Arch Gen Psychiatry.* 1995;52:895-899.

26. Wahlberg K-E, Wynne LC, Oja H, et al. Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish adoptive family study in schizophrenia. *Am J Psychiatry.* 1997;154:355-362.

27. Buka SK, Goldstein JM, Seidman LJ, et al. Prenatal complications, genetic vulnerability, and schizophrenia: the New England longitudinal studies of schizophrenia. *Psychiatric Annals.* 1999;29:151-156.

28. Geddes JR, Lawrie SM. Obstetric complications and schizophrenia: a meta-analysis. *Br J Psychiatry.* 1995;167:786-793.

29. Jablensky A. Schizophrenia: recent epidemiologic issues. *Epidemiol Rev.* 1995;17:10-20.

30. Lewis SW, Murray RM. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *J Psychiatr Res.* 1987;21:413-421.

31. Tsuang MT, Faraone SV. The case for heterogeneity in the etiology of schizophrenia. *Schizophr Res.* 1995;17:161-175.

32. Kendall RE, Juszczak E, Cole SK. Obstetric complications and schizophrenia: a case control study based on standardised obstetric records. *Br J Psychiatry.* 1996;168:556-561.

33. Cannon TD. Abnormalities of brain structure and function in schizophrenia: implications for etiology and pathophysiology. *Ann Med.* 1996;28:533-539.

34. Geddes J. Prenatal and perinatal risk factors for early onset schizophrenia, affective psychosis and reactive psychosis. *BMJ.* 1999;318:426.

35. Zornberg GL, Buka SL, Tsuang MT. Hypoxic ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psy-

choses: a 19-year longitudinal study. *Am J Psychiatry.* 2000;157:196-202.

36. Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case control study. *BMJ.* 1999;318:421-426.

37. Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. *Arch Gen Psychiatry.* 1999;56:234-240.

38. Torrey EF, Kaufmann CA. Schizophrenia and neuroviruses. In: Nasrallah HA, Weinberger DR, eds. *The Neurology of Schizophrenia.* Vol 1. Amsterdam, The Netherlands: Elsevier Science Publishers BV; 1986:361-376.

39. Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lonnqvist J. Association between prenatal exposure to poliovirus infection and adult schizophrenia. *Am J Psychiatry.* 1999;156:1100-1102.

40. Bogerts B. The temporolimbic system theory of positive schizophrenic symptoms. *Schizophr Bull.* 1997;23:423-435.

41. Rantakallio P, Jones P, Moring J, Von Wendt L. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. *Int J Epidemiol.* 1997;26:837-843.

42. Tsuang MT. Defining alternative phenotypes for genetic studies: what can we learn from studies of schizophrenia. *Neuropsychiatric Genet.* 2000. In press.

43. Moldin SO, Erlenmeyer-Kimling L. Measuring liability to schizophrenia: progress report 1994: editor's introduction. *Schizophr Bull.* 1994;20: 25-30.

44. Torgersen S. Relationship of schizotypal personality disorder to schizophrenia: genetics. *Schizophr Bull.* 1985;11:554-563.

45. Battaglia M, Torgersen S. Schizotypal disorder: at the crossroads of genetics and nosology. *Acta Psychiatr Scand.* 1996;94:303-310.

46. McGuffin P, Thapar A. The genetics of personality disorder. *Br J Psychiatry.* 1992;160:12-23.

47. Gunderson JG, Siever LJ, Spaulding E. The search for a schizotype: crossing the border again. *Arch Gen Psychiatry.* 1983;40:15-22.

48. Tsuang MT, Gilbertson MW, Faraone SV. Genetic transmission of negative and positive symptoms in the biological relatives of schizophrenics. In: Marneros A, Tsuang MT, Andreasen N, eds. *Positive vs Negative Schizophrenia.* New York, NY: Springer-Verlag. 1991:265-291.

49. Kendler KS, McGuire M, Gruenberg AM, Walsh D. Schizotypal symptoms and signs in the Roscommon family study. *Arch Gen Psychiatry.* 1995;52:296-303.

50. Grove WM, Lebow BS, Clementz BA, Cerri A, Medus C, Iacono WG. Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. *J Abnorm Psychol.* 1991;100:115-121.

51. Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV. Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophr Bull.* 1994;20:103-119.

52. Faraone SV, Kremen WS, Lyons MJ, Pepple JR, Seidman LJ, Tsuang MT. Diagnostic accuracy and linkage analysis: how useful are schizophrenia spectrum phenotypes? *Am J Psychiatry.* 1995;152:1286-1290.

53. Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Lyons MJ, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *J Abnorm Psychol.* 1995;104:286-304.

54. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. *J Abnorm Psychol.* 1999;108:176-181.

55. Toomey R, Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Tsuang MT. Association of vulnerability markers in relatives of schizophrenic patients. *Schizophr Res.* 1998;31:89-98.

56. Lyons MJ, Toomey R, Seidman LJ, Kremen WS, Faraone SV, Tsuang MT. Verbal learning and memory in relatives of schizophrenics: peliminary findings. *Biol Psychiatry.* 1995;37:750-753.

57. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Lyons MJ, Tsuang MT. Neuropsychological functioning among the elderly nonpsychotic relatives of schizophrenic patients. *Schizophr Res.* 1996;21:27-31.

58. Kremen WS, Goldstein JM, Seidman LJ, et al. Sex differences in neuropsychological function in nonpsychotic relatives of schizophrenic probands. *Psychiatry Res.* 1997;66:131-144.

59. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. *Biol Psychiatry.* 2000;48:120-126.

60. Tsuang MT, Stone WS, Seidman LJ, et al. Treatment of nonpsychotic relatives of patients with schizophrenia: four case studies. *Biol Psychiatry.* 1999;41:1412-1418.

61. Weinberger DR, DeLisi LE, Neophytides AN, Wyatt RJ. Familial aspects of CT scan abnormalities in chronic schizophrenic patients. *Psychiatry Res.* 1981;4:65-71.

62. Lawrie SM, Whalley H, Kestelman JN, et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet.* 1999;353:30-33.

63. Seidman LJ, Faraone SV, Goldstein JM, et al. Thalamic and amygdala-hippocampal volume reductions in first degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. *Biol Psychiatry.* 1999;46:941-954.

64. Siegel C, Waldo M, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives: evidence obtained with auditory evoked responses. *Arch Gen Psychiatry.* 1984;41:607-612.

65. Adler LE, Olincy A, Waldo M, et al. Schizophrenia, sensory gating, and nicotinic receptors. *Schizophr Bull.* 1998;24:189-202.

66. Waldo MC, Cawthra E, Adler LE, et al. Auditory sensory gating, hippocampal volume, and catecholamine metabolism in schizophrenics and their siblings. *Schizophr Res.* 1994;12:93-106.

67. Callicott JH, Egan MF, Bertolino A, et al. Hippocampal *N*-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biol Psychiatry.* 1998;44:941-950.

68. Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry.* 1999;45:395-402.

69. Adler LE, Hoffer LJ, Griffith J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biol Psychiatry.* 1992;32:607-616.

70. Stone WS, Rudd RJ, Gold PE. Glucose effects on scopolamine- and age-induced deficits in spontaneous alternation behavior and in regional [^{3}H]2-deoxyglucose uptake in mice. *Psychobiology.* 1992;20:270-279.

71. Ragozzino ME, Unick KE, Gold PE. Hippocampal acetylcholine release during memory testing in rats: augmentation by glucose. *Proc Natl Acad Sci USA.* 1996;93:4693-4698.

72. Stone WS, Seidman LJ, Wojcik J, Green AI. Glucose effects on cognition in schizophrenia. 29th Annual Meeting, Society for Neuroscience Abstracts. 1999;25:2074.