Schizophrenia: family studies and treatment of spectrum disorders

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

A substantial part of the contribution of genetic studies to the treatment of schizophrenia involves its emphasis on reliable and valid diagnoses. One consequence of this focus is the recognition that schizophrenic illness is broader than the diagnostic entity of schizophrenia itself, and instead consists of a "spectrum" of related disorders. Because some of the symptoms in these disorders differ from each other, they provide an opportunity to determine which ones reflect a common etiology. To the extent that such symptoms are identifiable, they may provide a foundation for treatment and even prevention strategies. In this paper, we focus on a clinical condition—"schizotaxia"—that may reflect the liability for schizophrenia. To characterize the nature and extent of this proposed syndrome, we will review results from family studies in our laboratory, and consider conceptual foundations and criteria for assessment. A more general consideration of treatment strategies for schizophrenia spectrum disorders follows, along with suggestions for future research. Our initial attempts to treat and validate schizotaxia are encouraging, and raise the possibility that early treatment might eventually prevent or attenuate the development of other, more severe disorders in the schizophrenia spectrum, including schizophrenia itself.

Keywords: *schizophrenia; spectrum disorder; schizotaxia; family study; schizotypal personality disorder; treatment*

It is over 100 years since Kraepelin delineated dementia praecox from manic depressive psychoses,[1] and nearly that long since Bleuler reformulated schizophrenia from dementia praecox.[2] In that time, progress toward effective treatments for schizophrenia has been slow, but tangible. At least three sources of progress are clearly identifiable. First, and most generally, treatments for schizophrenia and other mental illnesses have became more humane, and are now aligned more closely (although not closely enough) with treatments for other medical problems than used to be the case. Second, antipsychotic medications have become a first line of defense, and have improved the lives of most patients. This is particularly true of the newer generation of pharmaceutical agents.

Third, a greater understanding of the genetic basis of schizophrenia underlies much of our recent progress, in part through its focus on reliable and valid diagnoses. This paper will focus on one consequence of genetic studies, which is the recognition that schizophrenic illness is broader than the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* or *International Classification of Diseases (ICD)* diagnoses of schizophrenia, and exists as a "spectrum" of conditions. While some spectrum disorders are nearly as severe as schizophrenia (eg, schizoaffective disorder), others are milder and do not involve psychosis (eg, schizotypal personality disor-

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)

der [SPD]). The spectrum concept has numerous implications for treatment. For example, therapeutic efforts vary across schizophrenia spectrum disorders as functions of both the severity and the type of symptoms. These differences are of great importance in understanding the core features of schizophrenic conditions. In particular, the fact that psychosis is not a major feature of all schizophrenia spectrum disorders suggests that other, more subtle symptoms might better reflect the underlying etiology of schizophrenic illness, throughout the associated spectrum of disorders. If such deficits are identifiable, they may provide a foundation for treatment strategies. Moreover, if they are identified early, they may even prevent psychosis.

The discussion of spectrum disorders here will focus on symptoms that may reflect the genetic predisposition for schizophrenia. We reformulated Meehl's notion of "schizotaxia" recently to describe this liability,[3-5] and will review here studies conducted in our laboratory with nonpsychotic relatives of schizophrenic patients to conceptualize the nature and extent of this proposed syndrome. With schizotaxia in mind as a core liability for schizophrenia and other spectrum conditions, we will then consider treatments for spectrum disorders more generally, and directions for future research.

Lessons from family studies of nonpsychotic relatives of schizophrenic patients

Over the last 15 years, we have made steady progress toward the identification of neuropsychological and structural brain abnormalities among schizophrenic patients and their nonpsychotic first-degree relatives. Through the implementation of ongoing family studies, these data show: (i) the relatively specific neuropsychological deficits in schizophrenic patients and their relatives; (ii) the stability of these deficits over time; (iii) the structural and functional brain abnormalities in patients and relatives; and (iv) the effects of genetic loading on neuropsychological functions and neuroanatomical structures. These findings, which form the foundation of current efforts to define, validate, and treat schizotaxia, are described next.

Neuropsychological function among adult relatives

In an initial study, Faraone et al assessed neuropsychological functioning in 35 nonpsychotic adult relatives of schizophrenic patients and 72 normal controls.[6] We used linear combinations of neuropsychological tests to create scales assessing 10 neuropsychological functions: abstraction/executive function, verbal ability, spatial ability, verbal memory, visual memory, learning, perceptual-motor speed, mental control/encoding, motor function, and auditory attention. Based on previous neuropsychological studies of patients with schizophrenia and our review of family studies,[7] we predicted that relatives of patients with schizophrenia would exhibit deficits in abstraction/executive function, learning and memory, and components of attention (perceptual/motor speed, mental control/encoding, and vigilance).

A multivariate analysis of variance found the neuropsychological profile of the relatives to be significantly more impaired than the control profile. The relatives performed more poorly and had greater variability on the three predicted functions: abstraction/executive function, verbal memory, and auditory attention/vigilance. They had lower mean scores, but similar variability on verbal ability and mental control/encoding. They showed more variability, but not lower mean scores, on learning and motor abilities. The two groups did not differ in terms of visual/spatial ability, visual memory, or perceptual/motor function. The deficits observed were not accounted for by psychopathology in the relatives, by level of education, or by parental social class.

Because we did not study psychotic relatives, and only one of the relatives in our sample had SPD, we concluded that neuropsychological measures might be useful in detecting putative carriers of the schizophrenia genotype, who cannot be detected with psychiatric assessments. Our findings also led to the hypothesis that, if the expression of neuropsychological risk indicators in the relatives was due to an underlying genotype not present in the controls, then the neuropsychological indicators of the schizophrenia genotype would intercorrelate to a greater degree within the relative group than within the control group.[8] At the time of this more recent analysis, the sample had increased to 54 relatives of patients with schizophrenia. In the larger sample, the relatives continued to display significantly lower mean scores than the control group on abstraction skills, memory (verbal and visual), and auditory attention.

Within the relative group, we found significant intercorrelations among skills of abstraction, verbal memory, and auditory attention, both within and between these func-

tions. In addition, 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, the greater level of cooccurrence between these putative neuropsychological risk indicators within the high-risk group provides further support for their status as risk indicators of the same underlying vulnerability to schizophrenia.

Some recent studies[9] suggest that men with schizophrenia may have greater neuropsychological deficits than women. It is not known, however, whether similar sex differences may be present in biological relatives of patients with schizophrenia. We hypothesized that if sex differences were present, they would be accounted for largely by deficits in male relatives. We were particularly interested in the three neuropsychological functions that we identified as putative neuropsychological vulnerability indicators for schizophrenia. In fact, we found significant group-by-sex interactions for verbal memory and motor function, and trends toward significant interactions for auditory attention and mental control/encoding.[9] Notably, with the exception of motor function, it was the female relatives who accounted for most of the impairment. A speculative explanation for the findings is that women may have a higher threshold than men for developing schizophrenia. If so, female relatives might be able to withstand greater impairments than men before developing psychotic symptoms. Consequently, in a sample that was limited to nonpsychotic relatives, there could be overrepresentation of both less impaired men and more impaired women.

Stability of neuropsychological deficits

The neuropsychological studies discussed thus far used data from a baseline assessment. These were extended recently, in two ways.[10] First, by completing a follow-up study, we tested the hypothesis that neuropsychological deficits among adult relatives of schizophrenic patients would be stable over time. Second, with the addition of new tests of executive functioning, we tested the hypothesis that neuropsychological differences between controls and relatives of schizophrenic patients would be evident on delayed-response tasks. These tasks are sensitive to working memory, ie, the neuropsychological function that briefly holds information "on line" for use in other cognitive tasks such as reasoning. Differences between the groups included measures of immediate verbal memory, delayed verbal memory (both from the logical memory test), and complex attention (dichotic listening digits detected). Immediate and delayed verbal and visual memories showed interactions with gender, but none of the test scores showed group-by-time interactions, showing that the discriminating power of the tests remained stable over time. As we found at baseline, the relatives showed significantly poorer performance than the controls at follow-up.

For one of the additional tests of executive functioning, object alternation (OA), we found significant effects for sex and the group-by-sex interaction for the total and perseverative error scores. The nature of the interactions was the same as we observed at baseline: the greater impairment of relatives compared with controls was more pronounced for females than for males.

These results are consistent with the idea that neuropsychological dysfunction among relatives of schizophrenic patients is a stable trait that assesses the predisposition to schizophrenia.

Neuroimaging abnormalities

Structural magnetic resonance imaging studies

In addition to neuropsychological tests, relatives of patients with schizophrenia show abnormalities in both specific brain regions and patterns of brain activation.[11] In a pilot study,[12] we compared 6 female siblings of schizophrenic patients with 11 female controls. Volumes (ie, sizes of brain structures) were adjusted for total intracranial volume, which did not differ between the groups. Gray matter volumes of subcortical structures were smaller and ventricular volumes were larger among the relatives. Significant volume reductions in relatives were found in the thalamus, the right amygdala, the right pallidum, the right putamen, and the brain stem. Bilateral inferior lateral ventricles were significantly larger in relatives.

Interestingly, measures of auditory attention correlated with selected magnetic resonance imaging (MRI) brain volumes in this preliminary sample. In particular, total thalamus volume correlated with the ability to suppress interfering stimuli on two tests (r=0.87 and r=0.80), and total hippocampal volume correlated with the ability to handle a working memory load (r=0.89 and r=0.87) and with Wisconsin card sorting categories (r=0.70). These preliminary results suggest that interference effects on sustained attention are strongly associated with thalamus volume reduction, whereas attention, memory, and prob-

lem solving are associated with hippocampal volume reduction.

We recently completed analyses on a larger sample that includes schizophrenic patients.[13] We sought to extend our pilot study, and to determine which abnormalities characterized schizophrenic patients beyond those we had identified in the relatives. Subjects were 29 schizophrenic patients, 28 nonpsychotic first-degree adult relatives, and 26 normal controls. The volumes were adjusted for total cerebral volumes; statistical analyses were controlled for the effects of sex. Compared with controls, relatives had significant volume reductions bilaterally in the amygdala-hippocampal region, the thalamus, and the cerebellum, and significantly increased volumes in the pallidum.

Patients demonstrated significantly increased volumes in the lateral and third ventricles, the pallidum, and the right cerebral white matter. They had significant decreases in the left thalamus and the right hippocampus. Compared with relatives, patients had significantly larger putamen and amygdala-hippocampal regions and smaller cerebral cortices. Results indicate that nonpsychotic relatives of schizophrenic patients have abnormal brain structures that overlap with abnormalities in patients. This supports the hypothesis that the genetic liability to schizophrenia is expressed as brain abnormalities in key subcortical structures, including the thalamus and amygdala-hippocampal regions. These results are consistent with other studies of schizophrenic patients, in which third and lateral ventricle enlargements are the most common findings.

Our MRI data are consistent with the hypothesis that abnormalities in limbic-diencephalic areas may be core features of "schizotaxia," which become amplified by a second "hit" that alters the cortex, enlarges the third and lateral ventricles, and leads to schizophrenic illness. From these data, however, we are unable to determine whether the abnormalities found in patients reflect only greater preexisting pathology and thus a greater vulnerability to illness, or some additional pathology due to the progression of the illness or other incidental factors (ie, medications, etc). Eventually, studies of schizotaxia will help resolve this issue.

Functional MRI studies

In a preliminary study of normal subjects, our primary goal was to assess the brain activations (ie, brain areas that become activated) associated with simple and demanding auditory vigilance tasks, using functional MRI (fMRI).[14] We initially created novel auditory continuous performance tests (CPTs) in which a demanding working memory task was made more difficult than a simple vigilance task on the basis of increased working memory and interference filtering requirements. Compared with the vigilance task, performance of the working memory task produced significant signal changes bilaterally in the lateral prefrontal cortex, the premotor and frontal eye fields, the parietal-occipital cortex, the thalamus, the superior colliculus, the insula, the anterior cingulate, and the temporal lobe, including the hippocampus. Performance and degree of activation were associated with an IQ estimate.

We subsequently began a pilot study applying fMRI to the relatives of schizophrenic patients from our neuropsychology family study.[15] Thirteen never-psychotic and non–spectrum disorder relatives of schizophrenic patients and 12 matched normal controls were compared. All subjects were less than 55 years of age and had standard scores on a reading test of at least 80 (ie, at least the low-normal range). Relatives were significantly impaired on working memory tasks with interference. The tasks produced activation in the lateral and medial frontal cortex, the posterior parietal and precuneal cortex, and the thalamus in both groups. The most striking finding from these data is the difference in the number of regions activated and the extent of regional activations (number of "voxels") in relatives compared with the controls. Across the three tasks, the relatives had a greater number of activations, representing significantly more activated voxels than the controls. On working memory and memory plus interference tasks, activation was more bilaterally distributed in relatives than in controls. As relatives also perform worse on these cognitive tasks, these large and extraneous activations in relatives may represent: (i) compensatory exertion of inefficient neural circuitry in attempting to perform an effortful task to produce accurate output; and/or (ii) abnormal connectivity in the circuitry required to perform these tasks. These functional data complement the structural MRI abnormalities and suggest that adult relatives of schizophrenic patients have brain abnormalities, possibly associated with abnormal genes.

Effects of genetic loading on verbal memory and hippocampal volume in relatives

Following up the above findings of stability in measures of verbal memory and attention in nonpsychotic rela-

tives of schizophrenic patients, we compared individuals with one schizophrenic first-degree relative (simplex families) to individuals with two schizophrenic first-degree relatives (multiplex families).[16] Relatives from simplex families performed significantly less well on immediate memory (from the logical memory test) compared with controls, while relatives from multiplex families performed significantly worse on immediate and delayed logical memory, immediate visual reproductions, and estimated intelligence, compared with controls. Relatives from multiplex families also had a significantly poorer performance than relatives from simplex families on immediate and delayed logical memories, immediate visual reproductions, and estimated intelligence. These results are consistent with the idea that neuropsychological deficits in relatives of patients with schizophrenia reflect their degree of genetic predisposition to schizophrenia. This relationship was also evident in analyses of structural brain volumes. As described above, relatives show reduced hippocampal volumes compared with controls.[13,17] More recently, we found reductions in left (but not right) hippocampal volumes compared with controls, in both simplex and multiplex siblings of schizophrenic patients.[18] Multiplex siblings, however, also showed greater volume reductions than did simplex siblings. Moreover, better performance on the logical memory test was significantly correlated with larger hippocampal volume, especially on the left side, and especially in multiplex siblings. These data are further consistent with the hypothesis that greater degrees of genetic predisposition to schizophrenia are associated with neuropsychological (verbal memory) deficits and neurobiological abnormalities.

The nature of schizotaxia

Conceptual foundations

As noted above, Paul Meehl first used the term "schizotaxia" to describe the genetic predisposition to schizophrenia.[3] In his view, schizotaxic individuals would develop either schizotypy or schizophrenia, depending on environmental circumstances. For example, relatively favorable environmental conditions might interact with the genetic predisposition to produce schizotypy, while relatively adverse environmental conditions would more likely lead to schizophrenia. Meehl later modified his view somewhat to allow for the possibility that in some cases, schizotaxia might not progress to either schizotypy or schizophrenia, but this outcome represented the exception rather than the rule.[19] Eventually, schizotypy (in the form of SPD) entered the diagnostic nomenclature, but schizotaxia did not. Instead, it has been used mainly in research to indicate the premorbid, neurolobiological substrate of schizophrenia, but not used to identify a clinically meaningful syndrome or spectrum disorder.

Now, almost four decades later, research suggests that schizotaxia is a clinically consequential condition. A large body of evidence, including the examples described in the preceding section, shows abnormalities in affect, cognition, social functioning, and brain function among the nonschizotypal and nonpsychotic relatives of schizophrenic patients.[5] These data show that schizotaxia is not merely a theoretical construct; it has psychiatric and neurobiological features that justify further research about its nosologic validity.

Although our use of the term schizotaxia is consistent with Meehl's view of it as the underlying defect among people genetically predisposed to schizophrenia, we do not endorse several other aspects of his theory. Among these, first, is the nature of the genetic etiology of schizophrenia. For example, having written his theory prior to the availability of molecular genetic data, Meehl favored a single major gene theory of schizophrenia, which has since been falsified by genetic linkage studies. Second, Meehl viewed schizotaxia solely as the genetic predisposition to schizophrenia. We view schizotaxia as the predisposition to schizophrenia too, but conceptualize its etiology to include both genetic and nongenetic biological consequences of early adverse environmental circumstances (eg, pregnancy or delivery complications). Third, Meehl viewed schizotypy as the only nonpsychotic clinical expression of schizotaxia. In our view, schizotaxia is frequently a stable clinical condition that is more common in relatives of schizophrenic patients than is schizotypy. We found, for instance, that core symptoms of schizotaxia characterized 20% and 50% of nonpsychotic relatives of schizophrenic patients in our family studies.[6,20] Thus, schizotaxia does not necessarily progress into a more severe disorder.

This view of the liability for schizophrenia is consistent with a neurodevelopmental perspective. In our view, once schizotaxia develops, it may then interact with later adverse environmental events (considered broadly, such as substance abuse, psychosocial stressors, or a head

injury), which impairs brain function further and leads to psychosis. Psychosis itself is not necessarily caused by the same factors—genetic or environmental—that cause schizotaxia, but may reflect more of a nonspecific end-state that occurs in a variety of severe psychiatric and neurologic conditions (eg, major depression, severe head injury, partial complex seizures, Alzheimer's disease, and various substance-induced states). If this conceptualization of schizotaxia is correct, it may thus be a *more* specific expression of the predisposition to schizophrenia than is the ***DSM-IV*** diagnosis of schizophrenia. For this reason, if schizotaxia is validated as a syndrome, we proposed that the diagnosis of schizophrenia be broadened into two categories: schizotaxia, and schizotaxia plus psychosis (ie, schizophrenia).[4]

Assessment

Schizotaxia remains an evolving concept, not a disorder with set criteria. Tsuang et al[21] recently operationalized research criteria for schizotaxia based on the combination of negative symptoms and neuropsychological deficits, which are two of the most robust findings in first-degree relatives of patients with schizophrenia.[5,22] To meet the criteria of Tsuang et al for schizotaxia, subjects must show both moderate or higher levels of negative symptoms (defined as 6 scores rated 3 or higher on the Schedule for the Assessment of Negative Symptoms)[23] and neuropsychological impairment (defined as 2 standard deviations below normal in one cognitive domain, and at least 1 standard deviation below normal in a second cognitive domain) in tests of attention, long-term verbal memory, and executive function (eg, planning and abstraction).
These criteria are tentative and will require much research for their refinement and validation. Eventually, we assume that biological measures, such as structural or dynamic brain abnormalities, will come to be incorporated into the diagnosis. Tsuang's initial criteria for schizotaxia also required subjects to: (i) be first-degree relatives of patients with schizophrenia; (ii) speak English as a first language; (iii) have estimated IQ scores of at least 70; (iv) be between 19 and 50 years of age (the age range was partly related to administration of a treatment); and (v) provide informed consent to participate. Exclusion criteria were designed to minimize the influence of comorbid neurological, psychiatric, or other medical conditions (eg, head injuries, current substance abuse, or history of electroconvulsive treatments) that could mimic symptoms of schizotaxia. Individuals with any lifetime history of psychosis were excluded from the study.

Validation of the syndrome

The subjects described above also received several clinical interviews and rating scales in addition to tests and ratings for schizotaxia. This allowed us to begin to assess the concurrent validity of schizotaxia.[24] These additional measures included the Quality of Life (QOL) scale, the Social Adjustment Scale (SAS), the Symptom Checklist-90-Revised (SCL-90), the Physical Anhedonia (PA) scale, and the Global Assessment of Functioning (GAF) scale. The SAS, SCL-90, and PA scale were all self-rated, while the QOL and GAF scales were rated by the investigators. The investigator ratings were obtained blindly, as each subject's group assignment (schizotaxic or nonschizotaxic) was made later, after the independent criteria for schizotaxia were evaluated. Twenty-seven people received full evaluations for schizotaxia in the pilot study, of whom 19 did not meet criteria and 8 did. Performance on these supplementary scales was assessed by comparing subjects who met criteria for schizotaxia with those who did not. For both self- and investigator-rated scales, schizotaxic subjects showed consistently poorer clinical or social function in a variety of areas. They rated themselves as significantly more anhedonic on the PA scale than did the nonschizotaxic subjects. Schizotaxic subjects also showed a significantly higher global severity index on the SCL-90, and demonstrated particular elevations on the obsessive-compulsive, anxiety, and hostility subscales (other subscales, such as depression, paranoia, and psychoticism, did not differ between groups). Moreover, schizotaxic subjects rated themselves as significantly more impaired on several dimensions of social adjustment, as shown by lower scores on the family attachment factor of the SAS, and higher scores on the anxious ruminations factor. Consistent with these findings, schizotaxic subjects received significantly lower total ratings on the QOL scale, including the interpersonal relations subscale, and on the GAF scale. Because these findings show that schizotaxia is associated with independent measures of clinical and social function, they provide a measure of concurrent validity for our specific diagnostic criteria.

Treatment of spectrum disorders

Like schizophrenia, the schizophrenia spectrum disorders consist, to some degree, of a combination of the liability to schizophrenia (schizotaxia) and additional symptoms (eg, psychosis). Treatment, therefore, must address each of these components. This section will focus mainly on milder spectrum disorders, including SPD and schizotaxia, after a brief consideration of more severe conditions.

Psychotic disorders

Treatments for schizoaffective disorder are the same as those for schizophrenia and affective disorders alone. Due to the heterogeneous nature of schizoaffective disorder, we have found it useful to consider its psychopharmacological treatment in terms of its putative subtypes, including the affective (or bipolar) subtype, and the schizophrenic (or unipolar) subtype. Even with this division, the subtypes are probably not "pure," and are likely to include patients with related disorders. Schizoaffective disorder, affective type, is likely to include, in addition to patients with the correct diagnosis, some with bipolar affective disorder and some in excited states of schizophrenia. For these cases, treatment may include antipsychotic medication (eg, clozapine, risperidone, or olanzapine) and, possibly, mood stabilizers (eg, lithium) or anticonvulsants (eg, valproate or carbamazepine). It will be necessary in such cases to weigh the potential risks of such medications, such as elevated toxicity, against the potential benefits.

Treatment during intermorbid periods depends on the presence or absence of psychotic symptoms. Psychotic episodes in this period are associated with relatively poorer outcomes, and are likely to require chronic antipsychotic therapy.

Like the affective subtype, the schizophrenic subtype of schizoaffective disorder probably represents a combination of groups, including those with the correct diagnosis, along with some patients with a psychotic affective disorder, some patients with depressive forms of schizophrenia, some patients with bipolar disorder, and some patients with other conditions. Here again, combination treatments are likely to be more effective than a single treatment in these patients.

Nonpsychotic disorders

Schizotypal personality disorder

Although several personality disorders (PDs) may be related to the schizophrenia spectrum, including schizoid, paranoid, and schizotypal personality disorders, we focus on SPD because family studies show its genetic basis more clearly than they do in the other two conditions.[25,26] Some general therapeutic issues will be considered, followed by a review of outcome studies.

Patients with SPD often chronically view the world as an odd and threatening place, and thus may require extended courses of treatment.[27-29] Unfortunately, trust and rapport with the therapist—which are necessary for the success of any psychosocial therapy—are often difficult to establish. The frequent occurrence of paranoia and suspiciousness, together with social aloofness and constricted affect, make exploratory psychotherapeutic approaches less likely to bring about positive changes than approaches that emphasize supportive and cognitive–behavioral therapies.[27,29] In fact, these patients may only seek treatment to alleviate circumscribed problems, like anxiety or somatic complaints. Approaches that emphasize concrete, interim goals, and stipulate explicit means of attaining them, thus have the best chances of success. Because patients with SPD are vulnerable to decompensation during times of stress and may experience transient episodes of psychosis, they may also benefit from techniques to facilitate stress reduction (eg, relaxation techniques, exercise, yoga, and meditation). Fortunately, there is evidence that at least some individuals with schizotypal features are likely to seek treatment in times of stress.[30] In the short term, brief courses of antipsychotic treatment may be useful if symptoms of psychosis appear.

Because cognitive problems are also frequently amenable to concrete, goal-oriented approaches to treatment, SPD patients benefit from an understanding of their cognitive strengths and weaknesses, to help them confront and cope with long-standing difficulties in their lives. For example, problems in attention, verbal memory, or organizational skills contribute to failures in educational, occupational, and social endeavors, while reinforcing negative self-images and increasing performance anxiety. Knowledge of circumscribed cognitive problems allows patients to reframe their difficulties in a more positive manner, and facilitate selection of more realistic personal, educational,

and occupational goals. Moreover, specific cognitive deficits are often subject to at least partial remediation. For example, standard procedures are available to attenuate deficits in the acquisition, organization, and retrieval of new information (eg, writing information down in a notebook, using appointment books or planners, and rehearsing new information). Distractibility can be reduced by focusing on one task at a time, in contrast to switching back and forth between activities.

The value of specific treatments for psychiatric symptoms, however, is less clear, owing to a dearth of outcome studies involving psychotherapy, psychosocial, or psychopharmacological treatments for SPD. Published studies show methodological limitations (eg, small samples, subjects with mixed diagnoses, inadequate controls, and problems with internal validity), or provide outcome data on only limited aspects of the disorder. Nevertheless, it is clear that few treatment gains are evident from recent studies, which serves to reaffirm both the chronicity and the complexity of the disorder. This is particularly true of studies that utilized psychodynamically oriented therapy, either alone or in combination with other treatments (eg, group therapy or art therapy) as the primary treatment modality.

For example, McGlashan[31] studied former inpatients approximately 15 years after treatment, who were given retrospective DSM-III diagnoses. The study followed up former patients with a variety of diagnoses, including, among others, one third with pure SPD (n=10). Multiple outcome measures were employed. Because the main purpose of the study was to examine SPD as a diagnostic entity, there was little emphasis on assessing change in the same measures, which complicates any interpretation. The results showed, however, that most subjects with pure SPD functioned poorly at follow-up. On one measure of global functioning in which 0=continuously disabled and 4=normal, the mean score was 1.6.

Several studies investigated the usefulness of medications in treating SPD, although most investigations employed small numbers of subjects and combined samples of schizotypal and borderline PDs.[32,33] For these reasons, conclusions about the effectiveness of treatment must be conservative. Those studies in which results were reported for SPD separately from other PDs will be emphasized. Typical antipsychotic drugs have been proposed to reduce positive symptoms or depressed mood in times of acute stress, but the high incidence of adverse side effects has discouraged their widespread use at other times, including the more chronic, stable (ie, noncrisis) phases of the disorder.[27,32,34] Other types of medication, including fluoxetine,[35] have generally shown nonspecific effects.

Amoxipine, which has antidepressant and neuroleptic effects, was administered to a small group of personality-disordered patients that included 5 subjects diagnosed with *DSM-III* SPD.[36] After an average treatment duration of 39 days, significant reductions were evident in total scores on the Brief Psychiatric Rating Scale, and on the Hamilton Rating Scale for Depression. The authors hypothesized that the positive changes in this group were due to the neuroleptic properties of the medication.

Goldberg et al[37] administered thiothixene (an antipsychotic medication) to a group of patients that included, among others, *DSM-III* SPD (n=6). The Global Assessment Scale (GAS) and Hopkins Symptom CheckList-90 (HSCL-90) were among the measures used to assess treatment effects. At the end of 12 weeks of treatment, little therapeutic change was evident within the schizotypal groups, but modest improvements were observed in particular areas across groups, such as the psychotic and obsessive-compulsive scales of the HSCL-90.

Hymowitz et al[38] administered a low dose of haloperidol to 17 outpatients with *DSM-III* diagnoses of SPD, for 6 weeks. The initial dose of 2.0 mg was intended to rise to 12.0 mg, but side effects prevented administration of such a large increase, and the mean dose was 3.6 mg. Even with lower doses, 50% of the sample withdrew from the study because of side effects. Data analysis was performed on all 17 subjects when they had completed just 2 weeks of the protocol. Modest improvements were noted in some subscales of the Schedule for Interviewing Borderlines related to schizotypy (ie, ideas of reference, odd communications, and social isolation) and on GAS scores.

Taken together, the available literature on treatments for SPD offers few clearly effective treatments. The mechanisms of the few treatments that were somewhat effective are unknown. Interestingly, improvements in types of symptoms (eg, psychoticism) across diagnoses, rather than within them,[37] are consistent with the possibility that they may help at least some subgroups of patients. However, more psychopharmacological research is needed in this area, with larger, more homogeneous samples, to test the latter hypothesis. A review of the medications used in these studies also makes clear a need to find treatments that are well tolerated, and that target negative symptoms and cognitive deficits.

The value of such an approach is considered next, in relation to treatment strategies for schizotaxia.

Schizotaxia

The general therapeutic considerations discussed above in relation to SPD are relevant to schizotaxia as well. Because schizotaxia is related biologically to schizophrenia, we considered the possibility that effective treatments for schizophrenia would also be of value in schizotaxia. In particular, we hypothesized that schizotaxic deficits should respond to risperidone, a medication that improves negative symptoms and neuropsychological dysfunction in schizophrenic patients (see, for example, references 39 and 40). Thus, we completed an open drug trial in a small series of patients.

The clinical criteria for inclusion in the drug trial are described above.[21] Individuals who met these criteria for schizotaxia 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 6 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. In particular, 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 (the IQs of the other subjects ranged between 92 and 111). The cognitive and clinical improvements in 5 out of 6 individuals are encouraging and provide support for larger, more controlled trials. These preliminary findings are potentially important for several reasons. First, they suggest that several key clinical and neuropsychological symptoms in schizotaxic, first-degree relatives of patients with schizophrenia are reversible, at least in part. Moreover, they are reversible by a treatment that is effective against some of the same symptoms in schizophrenia, consistent with the view that these clinical symptoms may reflect elements that are common to schizophrenia. Second, they show that impairments in such individuals may be ameliorated safely with risperidone. These results are preliminary and require replication in larger, controlled studies before they can be considered as a basis for treatment. Such studies are currently in progress.

Future directions

Because the familial basis of schizophrenia spectrum disorders reflects a genetic relationship to schizophrenia, we might predict that current, effective treatments for schizophrenia would also be useful in the treatment of these disorders. Moreover, family studies of schizotaxia suggest at least three pertinent directions for future research. First, our initial findings with risperidone treatment suggests that pharmacological treatments for spectrum disorders need not be limited to periods of crisis and decompensation, but could also be aimed at the chronic components of the disorders as well. Second, schizophrenic illness is not limited to positive symptoms, but includes negative symptoms, neuropsychological deficits, and neurobiological abnormalities. Consequently, treatment strategies need to determine whether these symptoms are treatable. Our findings with risperidone in schizotaxic relatives suggest that at least some of these symptoms can be attenuated. Third, and perhaps most significantly, treatments for schizotaxia have the potential to attenuate or even prevent the development of other, more severe, disorders in the spectrum of schizophrenia. An important goal for the near future is the need to characterize and validate schizotaxia as a syndrome. Eventually, however, treatments for schizotaxia might be administered to high-risk individuals to prevent the onset of nonpsychotic spectrum conditions and schizophrenia itself. ❑

Estudios familiares y tratamiento del espectro esquizofrénico

Una parte sustancial de la contribución de los estudios genéticos al tratamiento de la esquizofrenia se refiere al énfasis en la confiabilidad y validez del diagnóstico. Una consecuencia de este enfoque es reconocer que la enfermedad esquizofrénica es más amplia que la entidad diagnóstica de la esquizofrenia como tal, y más bien consiste en un "espectro" de trastornos relacionados. Ya que algunos de los síntomas de estos trastornos difieren unos de otros, ellos dan la oportunidad de determinar cuáles reflejan una etiología común. En la medida que estos síntomas sean identificables, ellos podrán aportar un fundamento al tratamiento e incluso estrategias de prevención. En este artículo nos enfocamos en una condición clínica – "la esquizotaxia" – la que puede reflejar el riesgo para la esquizofrenia. Para caracterizar la naturaleza y dimensión de este síndrome propuesto se revisarán los resultados de estudios familiares en nuestro laboratorio y las bases conceptuales y criterios de evaluación. Se continuará con una consideración más general acerca de las estrategias terapéuticas del espectro esquizofrénico junto con sugerencias para futuras investigaciones. Nuestros intentos iniciales para tratar y validar la esquizotaxia son alentadores y auguran posibilidades que el tratamiento precoz pueda eventualmente prevenir o atenuar otros trastornos más severos del espectro esquizofrénico, incluida la esquizofrenia propiamente tal.

Études familiales et traitement du spectre des désordres associés à la schizophrénie

Les études génétiques participent de façon importante au traitement de la schizophrénie en contribuant à l'établissement d'un diagnostic sérieux et valide. Ceci entraîne la reconnaissance que la pathologie schizophrénique dépasse largement le cadre de l'entité diagnostique de la schizophrénie elle-même, pour inclure tout un spectre de désordres associés. Du fait que ces désordres entraînent des symptômes dont certains présentent des différences nettes les uns par rapport aux autres, il est possible de déterminer lesquels reflètent une étiologie commune. Dans la mesure où ces symptômes sont identifiables, ils peuvent servir de base à des stratégies thérapeutiques ou même préventives. Dans cet article nous nous sommes essentiellement intéressés à un état clinique, "la schizotaxie", qui pourrait traduire la prédisposition à la schizophrénie. Dans le but de caractériser la nature et l'étendue du syndrome ainsi défini, nous examinerons les résultats provenant d'études familiales effectuées dans notre laboratoire, tout en évoquant quelles en sont les bases conceptuelles et les critères d'évaluation. Suivront des considérations plus générales sur les stratégies thérapeutiques concernant les désordres appartenant au spectre de la schizophrénie ainsi que des propositions pour la recherche future. Nos premiers essais concernant le traitement et la validation de la schizotaxie sont encourageants et suggèrent qu'il est possible, grâce au traitement précoce, d'atténuer, voire de prévenir le développement d'autres désordres plus sévères appartenant au spectre de la schizophrénie, voire la schizophrénie elle-même.

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