Towards the Prevention of Schizophrenia

Ming T. Tsuang, William S. Stone, and Stephen V. Faraone

There is a growing emphasis on attempts to identify the early signs and symptoms of schizophrenia, largely because early detection and treatment of psychosis (i.e., secondary prevention) are associated with relatively favorable clinical outcomes. This raises the issue of whether prevention of psychosis itself is possible. The achievement of this goal will require the identification of a premorbid state that could serve as the foundation for treatment strategies aimed ultimately at the prevention of schizophrenia. Fortunately, evidence for such a state is emerging, in part because schizophrenia may result from a neurodevelopmental disorder that is associated with a variety of clinical, neurobiological, and neuropsychologic features occurring well before the onset of psychosis. These features may serve as both indicators of risk for subsequent deterioration and the foundation of treatment efforts. We reformulated Meehl’s term schizotaxia to describe this liability and discuss here how its study could form the basis for future strategies of prevention. We also include a description of our initial attempts to devise treatment protocols for schizotaxia. It is concluded that schizotaxia is a feasible concept on which to base prevention efforts, and that treatment of adult schizotaxia may be among the next steps in the process. Biol Psychiatry 2000;48:349–356 © 2000 Society of Biological Psychiatry

Key Words: Schizotaxia, genetics, negative symptoms, neuropsychology, risperidone

Introduction

During the past decade, researchers have focused schizophrenia treatment studies on the early treatment of psychosis. Wyatt’s (1995) review of 21 controlled studies found that patients who had been treated with antipsychotic medicine during their first or second hospitalization had a better outcome than patients who had not been treated early in the course of illness. Others have suggested that early treatment, especially with newer agents, might preserve brain plasticity and reduce the clinical deterioration of chronic schizophrenia (Green and Schildkraut 1995; Lieberman 1996; McGlashan and Johannessen 1996). It is also possible that, rather than having a neuroprotective effect, early treat- ment mitigates the social consequences of schizophrenic psychopathology, which may result in better outcome by allowing for the easier reintegration of patients into their social networks. In fact, it may help prevent patients from losing these networks in the first place. These lines of reasoning have motivated the creation of early detection and intervention projects seeking to treat schizophrenic patients during their prodrome or first episode (Falloon et al 1996; Green and Schildkraut 1995; McGlashan 1996; McGlashan and Johannessen 1996; McGorry et al 1996; Olin and Mednick 1996; Vaglum 1996; Yung et al 1996).

The treatment of incipient psychosis is an outstanding secondary prevention strategy. But will it be enough? The compelling reasons for pursuing secondary prevention also provide compelling reasons for developing primary prevention protocols. There are, however, two reasons why the progress toward the primary prevention of schizophrenia remains in its infancy. First, we cannot implement a primary prevention protocol unless we can accurately define the population at risk for schizophrenia. Second, we must have a solid rationale for any proposed preventive treatment.

In this review, we outline an approach to these issues by focusing on “schizotaxia,” a term that Meehl (1962, 1989) introduced to describe the predisposition to schizophrenia and Faraone et al (in press) modified to fit with data collected since Meehl’s formulation. We begin with a brief discussion of the role of prevention in schizophrenia, and then outline the concept of schizotaxia. This leads to a consideration of how research into schizotaxia could facilitate the development of strategies for the primary prevention of schizophrenia, followed by a description of our initial steps towards this goal, which include the establishment of research protocols for the treatment of schizotaxia in adults.

Early Identification and Treatment of Schizophrenia

Although 100 years of research have not produced a cure for schizophrenia, we have made significant progress in its diagnosis and treatment, and in our understanding of its
underlying neurobiology. A substantial portion of this credit goes to the development of antipsychotic drugs. Successive generations of these agents have had an enormous beneficial effect on the lives of patients and their families. Despite progress in treatment, there is clearly a long way to go before the symptoms of schizophrenia are fully “controlled” in most patients, in the sense that normal clinical and cognitive functions are restored (or attained). Thus, researchers have been testing secondary prevention strategies, which focus on the early detection and treatment of the disorder. In 1938 Cameron (cited in McGorry et al 1996) first described the need to treat schizophrenia early to prevent subsequent deterioration. Since then, evidence has accumulated to support the view that the longer treatment is delayed, the poorer is the subsequent prognosis (Green and Schildkraut 1995; Wyatt 1995; Wyatt et al 1996).

Several benefits of early treatment are likely, including the prevention of the social, interpersonal, cognitive, and affective disruptions that accompany and follow the initial psychotic episode. One potential consequence of secondary prevention is simply the delay of onset. This may be especially valuable for early-onset cases, as these patients would then have more time to mature before having to cope with a serious and chronic illness. Moreover, untreated schizophrenia may become more resistant to treatment, in part because psychosis itself may create widespread neurobiological abnormalities (Knoll et al 1998) that, at best, complicate current treatment strategies. If the early treatment of psychosis mitigates the course of schizophrenia, implementing early identification and treatment programs should be valuable because psychotic symptoms are present for an average of about 2 years before treatment is sought (e.g., Loebel et al 1992).

Research and theory about the early treatment of psychosis naturally lead to the question, can psychosis be avoided? Most researchers have approached the issue by focusing on prodromal symptoms as indicators of an impending psychotic disorder, but the issue is far from straightforward. McGorry et al (1995) showed, for example, that DSM-III-R prodromal symptoms for schizophrenia occurred in 15–50% of high school students. This raises obvious questions about the validity of intervening on the basis of such symptoms. Are prodromal symptoms like social withdrawal, or subtle changes in thinking or affect, valid enough indicators of early schizophrenia to warrant intervention, possibly with antipsychotic medications and their associated side effects? Do such nonspecific symptoms warrant the potential anxiety and stigmatization (for both “patients” and their families) that might attend the classification of an individual as likely to develop schizophrenia, probably in the near future? Unfortunately, these questions cannot yet be answered in the affirmative. There is little clear evidence that prodromal symptoms are specific for schizophrenia or for other psychotic illness (Larsen and Opjordsmoen 1996). Given this state of affairs, the risks of primary prevention programs are magnified even further if high-risk status is assigned and interventions are proposed before clinical symptoms emerge.

Our current state of knowledge, then, appears to preclude the application of preventative treatments for people without clinical symptoms of psychosis, or at least the prodrome. If this is so, how might prevention strategies proceed?

**Schizotaxia: Toward a Definition of “Preschizophrenia”**

The concept of schizotaxia was first introduced by Meehl to describe a “neural integrative defect” that was the neurobiological consequence of the schizophrenia’s genetic origins (Meehl 1962). In other words, schizotaxia was intended to describe the genetic vulnerability to schizophrenia. Meehl suggested that all individuals with schizotaxia would, through the normal processes of social learning, develop schizotypal personality structures. Depending on the protection or liability afforded by environmental circumstances, a minority of these individuals would decompensate and develop schizophrenia. Over the next 25 years, Meehl revised the concept to allow for the possibility that some people with schizotaxia would develop neither schizophrenia nor schizotypal personality disorder (Meehl 1989). Although the term *schizotaxia* achieved popularity in the research literature as a broad description of clinical or biological features thought to reflect the genetic liability for schizophrenia, it did not enter the clinical psychiatric nomenclature.

Now, over 30 years later, the accumulated evidence shows that the liability for schizophrenia can be characterized clinically by deficits in psychiatric, neuropsychologic, neurobiological, and psychosocial domains, in non-psychotic, first-degree relatives of people with schizophrenia. Clinical psychiatric features in such relatives frequently include negative symptoms that are similar qualitatively, but milder quantitatively, than those observed frequently in schizophrenia (Tsuang et al 1991). Positive symptoms, however, are usually less evident in these relatives than they are in schizophrenia or in schizotypal personality disorder. We stress that the symptoms of schizotaxia are distinct from the symptoms of the prodrome, and typically appear well before the onset of prodromal symptoms. Neuropsychologic impairments in biological relatives of people with schizophrenia are also similar to, but milder than, those that occur in schizophrenia (Faraone et al 1995b, in press; Kremen et al 1994; Park...
et al 1995). Particular areas of deficit frequently include attention/working memory, long-term verbal memory, and executive functions.

Recently we suggested modifications to the concept of schizotaxia that focused on negative symptoms and neuropsychologic deficits (Faraone et al, in press; also see Table 1 for a summary of our tentative research criteria for the assessment of schizotaxia). Our empirical analyses showed that the percentage of adult relatives who demonstrated these features among first-degree biological relatives of schizophrenic patients is substantial. Unlike schizotypal personality disorder, which occurs in less than 10% of the adult relatives of patients diagnosed with schizophrenia (Battaglia and Torgersen 1996), and schizophrenia, which occurs in about 10% of first-degree relatives (Gottesman 1991), these basic symptoms of schizotaxia occur in 20–50% of adult relatives (Faraone et al 1995a, 1995b, in press). These findings indicate that the genetic liability to schizophrenia does not lead inevitably to either schizophrenia or schizotypal personality disorder.

Our concept of schizotaxia has several advantages. One is its usefulness for genetic studies (Faraone et al 1999). If the proportion of first-degree relatives with schizotaxia is larger than the proportions of relatives with other related conditions (like schizotypal personality disorder or schizophrenia), then the classification of schizotaxia may allow for a more accurate differentiation of individuals who are genetically “affected” from those who are not (for a review of the technical aspects of this issue, see Faraone et al 1995a). Second, the utilization of neuropsychologic symptoms in our reformulation emphasizes “endophenotypic” measures (Gottesman 1991) that are more proximal to their underlying genetic/biological etiologies than are the relatively end-state clinical symptoms that define schizophrenia and schizotypal personality disorder. Third, and most relevant for this discussion, schizotaxia extends the spectrum of liability to schizophrenia to a clinically meaningful but premorbid state. This makes it ideal for identifying preschizophrenic persons and for designing primary prevention strategies for schizophrenia.

Although our initial characterizations of schizotaxia are encouraging, it is an evolving concept rather than a strictly defined diagnostic condition. As noted above, the concept needs to be validated empirically, and criteria sets need to be established to differentiate it reliably from potentially comorbid conditions like schizotypal personality disorder. It is also likely that schizotaxia will come to incorporate biological measures of dysfunction caused by combinations of schizophrenia genes and adverse environmental events.

Our view of schizotaxia is consistent with neurodevelopmental models of schizophrenia. Consistent with other neurodevelopmental hypotheses (Goldman-Rakic 1995; Seidman 1990; Weinberger 1995a, 1995b), we hypothesize that a combination of genes and environmental events leads to altered development of the brain, perhaps as early as the second trimester of life. This combination results in schizotaxia, which is a neurodevelopmental syndrome that is characterized by neuropsychologic and neurobiological dysfunctions, the latter of which may include reduced volumes in several brain areas, and/or altered patterns of brain activation in response to external challenges or stimuli (Seidman 1997).

Evidence in favor of neurodevelopmental hypotheses in schizophrenia is extensive (e.g., Beauregard and Bach优雅 1996; Faraone et al, in press; Tsuang and Faraone 1995; Tsuang et al 1991; Weinberger 1995a, 1995b; Woods 1998). Briefly, it includes 1) studies showing elevated rates of pregnancy and/or delivery problems, and exposure to viruses; 2) postmortem studies showing brain abnormalities indicative of second or third trimester problems of development; 3) animal models demonstrating that neonatal hippocampal lesions produce effects that are not fully apparent until adulthood; 4) neuropsychologic deficits in nonpsychotic, first-degree relatives of patients with schizophrenia; 5) elevated rates of negative, but not positive, symptoms in schizophrenia families; and 6) evidence of brain volume loss before the onset of psychotic symptoms in some schizophrenic patients. Most of this evidence is consistent with the view that at least some significant aspects of the premorbid substrate of schizotaxia...
phrenia are formed before the onset of the illness. Negative symptoms and neuropsychologic deficits in family members, for example, are significant because they occur in schizophrenia, and in some family members who later develop schizophrenia or a related disorder. The extent to which factors like pregnancy and delivery complications increase the liability for schizophrenia remains to be established, as does their specificity, although a variety of studies have shown them to be elevated in schizophrenic patients (Zornberg et al 2000). Evidence for prenatal viruses is less clear, but remains suggestive (Tsuang and Faraone 1995).

Our view of schizotaxia fits in with another feature of the neurodevelopmental models noted above. For reasons that remain unknown, the syndrome sometimes results in psychosis (i.e., schizophrenia) and sometimes does not. Moreover, the notion of schizotaxia as a neurodevelopmental disorder with genetic and environmental etiologic components, and variable outcomes, also parallels diathesis/stress conceptualizations of the origins of schizophrenia (Gottesman 1991). Each of these views emphasizes the importance of genetic/biological risk factors for schizophrenia. If, as suggested above, these factors constitute the premorbid substrate of the disorder, then it may be possible to intervene therapeutically before schizophrenia emerges. Because early treatment is associated with better outcomes, these views are thus consistent with the hypothesis that successful treatments of schizotaxia will modify or even prevent its subsequent progression to a more severe disorder, such as schizophrenia.

The Schizotaxia Treatment Protocol: A Prelude to Prevention

One key to the prevention of schizophrenia will be the identification of abnormalities that reflect the etiologic processes that lead to the onset of psychosis. This means that, in addition to assessing clinical symptoms, there is a need for assessing areas of dysfunction that are closer than clinical symptoms to the etiologic process that ultimately causes schizophrenia. Indeed, a significant weakness of the reliance on prodromal symptoms, and one that is related to their lack of prognostic specificity, is that they often reflect relatively distal effects of etiologic processes. Fortunately, we are at a point where we are not limited to the use of clinical symptoms alone to identify the vulnerability for schizophrenia.

Given the hypothesis that features of schizotaxia reflect the predisposition to schizophrenia, what steps must be taken to design a strategy aimed at preventing schizophrenia? Clearly, the validity of schizotaxia as a predictor of subsequent schizophrenia must be firmly established. As Robins and Guze (1970) pointed out, it is crucial to establish both the concurrent and predictive validities of putative syndromes. Does the classification of schizotaxia predict neuropsychologic, neuroimaging, or psychophysiological findings that are consistent with what is known about the neurobiology of schizophrenia? As we have reviewed elsewhere, a growing body of literature suggests that the answer is yes (Faraone et al, in press). Abnormalities found among relatives of schizophrenic patients include eye-tracking dysfunction (Levy et al 1994), allusive thinking (Catts et al 1993), neurologic signs (Erlenmeyer-Kimling et al 1982), characteristic auditory-evoked potentials (Friedman and Squires-Wheeler 1994), neuroimaging-assessed brain abnormalities (Seidman et al 1997), and neuropsychologic impairment (Kremen et al 1994).

More importantly, does schizotaxia predict the subsequent emergence of psychotic symptoms or other forms of psychopathology? Studies of children at risk for schizophrenia show that schizotaxic features do predict subsequent schizophrenia and related disorders (Auerbach et al 1993; Dworkin et al 1994; Erlenmeyer-Kimling 2000; Ingraham et al 1995; Olin and Mednick 1996; L. Erlenmeyer-Kimling, personal communication, 1997). But more work is needed to create measures of schizotaxia that will accurately classify children who do and do not go on to become schizophrenic. It should be noted that the issue of risk factors in schizotaxia also raises the issue of “protective” factors to mitigate them. Like risk factors, protective factors may be genetic/biological and/or environmental (Tsuang 2000). We use the term here to describe independent factors that reduce risk, rather than using it to describe the absence of factors that confer risk. This is an intriguing notion that has been difficult to pursue (deficits have been more amenable to detection), but that will hopefully “come of age” with advances in technology.

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

The use of the schizotaxia treatment protocol assumes that the syndrome of schizotaxia observed among first-degree relatives of schizophrenic patients shares etiologic
and pathophysiologic pathways with preschizophrenic people. If this assumption is true, then any medication that targets these pathways to mitigate schizotaxic features may also work to reduce the likelihood of the onset of psychosis. This assumption is reasonable because 1) first-degree relatives of schizophrenic patients are at high risk for carrying schizophrenia susceptibility genes (Gottesman 1991) and 2) the features of schizotaxia observed among these relatives are similar to the features of schizotaxia seen in children who eventually become schizophrenic (Faraone et al, in press).

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

We view the schizotaxia treatment protocol as a model system for testing hypotheses about primary prevention. It is a model because only some elements of the risk for schizophrenia are present. This is analogous to the use of animal models of disorders that attempt to define and manipulate specified components of the system. Such models are useful in that they facilitate focused analyses of the behavior of simpler systems. Moreover, models are often necessary because the ultimate goal of the research is not yet amenable to study for other reasons. In the case of prevention research for schizophrenia, the ethical and safety concerns about identifying and treating “high-risk” children still outweigh the benefits of proceeding with such studies. Eventually, however, as elements are incorporated into the models, the comprehensiveness of the system, and its approximation to the condition of interest, increases. In this case, our model of the prevention of schizophrenia starts out as the treatment of clinically meaningful symptoms in schizotaxia, in adults.

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

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

Tsuang et al (1999) recently described a working definition of schizotaxia based on a set of specific criteria, for the purpose of developing a treatment protocol. Table 1 shows our initial research criteria for the diagnosis of schizotaxia.

The cognitive domains included vigilance/working memory, long-term verbal memory, and executive functions. Specific tests and measures on tests were used to meet the neuropsychologic criteria (Tsuang et al 1999). Our decision to require moderate deficits in different domains ensured that our initial treatment attempts would include only adults with demonstrable clinical and neuropsychologic difficulties. This was important both to demonstrate the clinically meaningful nature of schizotaxia and to make the risk/benefit assessment of treatment more favorable. Although we wanted to start with a restrictive set of criteria, it is likely that modifications will be necessary in order to conduct large-scale studies. Some of the exclusion criteria in particular, like that involving substance abuse diagnoses, may need to be altered if requisite numbers of subjects are to be enrolled in research protocols. Nevertheless, the stringent nature of the criteria underscores the clinical meaningfulness of schizotaxia and the potential importance of developing treatment protocols to attenuate it, independent of its value as a strategy to prevent schizophrenia.

Our first application of the schizotaxia treatment protocol (Tsuang et al 1999) used risperidone, a novel antipsychotic medication. As we noted above, trials of these medications would appear reasonable on the basis of our assumption that individuals with schizotaxia share etiologic and psychopathologic elements with schizophrenia. Trials with the older, typical antipsychotics, however, were limited by reluctance to use these medications in nonpsychotic populations, mainly because of their side effects and subsequently high rates of noncompliance (Hymowitz et al 1986), but also because of their essential inability to alleviate negative symptoms (Marder and Meibach 1994) or neuropsychologic deficits (Cassens et al 1990).

Another reason we chose risperidone was that, compared with other novel antipsychotics medications, it had (at the inception of the study) been shown to reduce positive and some negative symptoms in schizophrenia (Marder and Meibach 1994; Rossi et al 1997; Tamminga 1997). It was clearly safer than typical neuroleptics, in that it produced fewer extrapyramidal side effects (at least at lower doses; e.g., Marder and Meibach 1994; Tamminga
1997). Notably, it also improved cognitive functions in schizophrenia, especially in attention or working memory (Green et al 1997; Rossi et al 1997; Stip 1996), but possibly in verbal long-term memory (Stip 1996) and executive functions (Rossi et al 1997) as well. This latter feature was especially important given that neuropsychologic impairment is a hallmark of schizotaxia.

Based on these issues, we began an open trial of risperidone with people who met our criteria for schizotaxia (Tsuang et al 1999). After all entrance criteria were met, subjects received low doses (starting at 0.25 mg and reaching maximum doses of 2.0 mg) of risperidone for 6 weeks. During that period they were evaluated weekly for side effects and for clinical and neuropsychologic effects of treatment. After 6 weeks most clinical and neuropsychologic tests were repeated. We reported on the effects of treatment in our first four cases (Tsuang et al 1999) and have since completed two additional cases. Five out of six cases showed marked improvements in a demanding test of auditory attention (improvements were 1.5–2.0 SDs in magnitude, which placed subjects in the normal range of performance), and all subjects showed reduced negative symptoms after 6 weeks. In three cases, reductions in negative symptoms were marked (approximately 50% reductions in total Scale for the Assessment of Negative Symptoms scores), whereas in two they were modest (25% reductions). One individual did not improve in either cognition or negative symptoms. Interestingly, this subject had lower overall cognitive abilities (an IQ of 75) than did the other cases (IQs ranged from 92 to 111). Her low test scores may thus represent the effect of two interrelated but distinct problems: schizotaxia and low cognitive abilities.

In this view, the treatment may have been effective against symptoms of schizotaxia, but ineffective against the more general problem of limited intellectual abilities. Consequently, this subject did not improve with treatment.

Side effects, when they occurred, were mild to modest in severity. No one requested the discontinuation of treatment, but in some cases the doses were lowered to reduce discomfort. Side effects tended to differ between cases, but included symptoms such as dry mouth, sedation, and weight gain.

Future Directions

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

Despite this caveat, our findings suggest the feasibility of developing treatment strategies for adult schizotaxia. It is clear that we are only starting this process. Perhaps the most important task for the near future, in addition to the need for more methodologically rigorous replications, is the validation of schizotaxia as a syndrome. This process will likely include the eventual incorporation of additional clinical, neurobiological, neuropsychologic, and neurodevelopmental measures. At some point it will also include molecular biological data, as the genes that cause schizotaxia are located. As the validity of schizotaxia becomes established, the risk (for subsequent psychosis) provided by its component features will become measurable. That knowledge base will provide the foundation for strategies aimed at the prevention of schizophrenia, hopefully in the not too distant future.

References

Andreasen NC (1983): The Scale for the Assessment of Negative Symptoms (SANS). Iowa City: The University of Iowa.


Prevention of Schizophrenia


Tsuang MT, Gilbertson MW, Faraone SV (1991): Genetic transmission of negative and positive symptoms in the biological relatives of schizophrenics. In: Marneros A,


