Understanding Predisposition to Schizophrenia: Toward Intervention and Prevention

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Objective: Early intervention to prevent schizophrenia is one of the most important goals of schizophrenia research. However, the field is not yet ready to initiate trials to prevent prodromal or psychotic symptoms in people who are at risk for developing the disorder. In this paper, we consider some of the major obstacles that must be studied before prevention strategies become feasible.

Method and Results: One of the most important hurdles is the identification of a syndrome or set of traits that reflects a predisposition to schizophrenia and that might provide potential targets for intervention. In a recent reformulation of Paul Meehl's concept of schizotaxia, we integrate research findings obtained over the last 4 decades to propose a syndrome with meaningful clinical manifestations. We review the conceptualization of this syndrome and consider its multidimensional clinical expression. We then describe preliminary research diagnostic criteria for use in adult, nonpsychotic, first-degree relatives of patients diagnosed with schizophrenia, based on negative symptoms and neuropsychological deficits. We follow this with evidence supporting the validity of the proposed syndrome, which mainly includes social dysfunction and response to a low dosage of one of the newer antipsychotic medications.

Conclusions: Continued progress toward the eventual initiation of prevention strategies for schizophrenia will include sustained efforts to validate the traits reflecting a predisposition to develop the disorder (for example, schizotaxia), follow-up studies to confirm initial findings, and the identification of potentially useful preventive interventions.

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Clinical Implications

- The predisposition to develop schizophrenia in nonprodromal, nonpsychotic adult relatives of patients with schizophrenia may be expressed as a meaningful, diagnosable, clinical syndrome or set of traits, called schizotaxia.
- In adults, at least some schizotaxia symptoms may be attenuated with interventions.
- Interventions that attenuate schizotaxia symptoms in adults may eventually be useful in strategies aimed at preventing schizophrenia.

Limitations

- Double-blind intervention studies of schizotaxia are needed.
- Longitudinal neuroimaging data are needed for children at high risk for developing schizophrenia.
- Molecular-genetic studies of schizotaxia are needed to extend and validate the syndrome.

Key Words: *schizophrenia, schizotaxia, genetics, negative symptoms, neuropsychological deficits, schizotaxia treatment protocol*

Schizophrenia is a neurobiologically based disorder whose etiology is rooted in a combination of genetic and environmental risk factors (1). At-risk individuals often manifest this liability clinically, in the form of psychiatric symptoms and neurobiological abnormalities, without fully developing schizophrenia. Characterizing the predisposition for schizophrenia is important from both a clinical and a research perspective. For example, identifying individuals who have this liability affords us the opportunity to develop interventions aimed at alleviating its clinical manifestations. Moreover, the study of adult relatives of schizophrenia patients who carry the risk, but who are without psychosis and do not develop schizophrenia, could aid in identifying which individuals will or will not develop the disorder. As the accuracy of prediction increases, the potential for preventing schizophrenia onset moves closer to reality.

However, the field is not yet ready to initiate treatment strategies. In this article, we focus on issues that may serve as preludes to intervention; resolving them will help us to develop viable approaches to prevention. In particular, we focus on a concept of the predisposition for schizophrenia called "schizotaxia" and on the use of a schizotaxia intervention protocol to evaluate treatments that may be potentially useful for preventing schizophrenia. We begin by reviewing the concept of schizotaxia and examining its clinical expression in nonpsychotic relatives of patients with schizophrenia.

The Concept of Schizotaxia

In 2001, starting from the premise that the neurobiological basis of schizophrenia comprises the combined effect of genes and adverse environmental risk factors, we proposed a modified view of Paul Meehl's concept of schizotaxia to describe a neurodevelopmental condition underlying the predisposition to schizophrenia (2). In 1962, Meehl used the term to characterize the genetic predisposition to schizophrenia, which he thought was rooted in a "neural integrative defect" (3). As a result of inherited factors (for example, a predisposition to high or low anxiety) and environmental influences, including the effects of social learning, vulnerable individuals developed schizotypy. Where environmental and genetic circumstances were favourable, the clinical symptoms were minor (that is, "compensated schizotypy"), but less favourable circumstances resulted in more severe conditions, including schizophrenia. The term schizotypy (in the form of schizotypal personality disorder [SPD]) eventually entered the diagnostic nomenclature, but schizotaxia did not. It has been used in research to indicate the premorbid, physiological substrate of schizophrenia, but it has not been examined as a clinical syndrome. However, considerable research now suggests that schizotaxia is a clinically consequential condition. Abnormalities in affect, cognition, and social functioning among the nonschizotypal and nonpsychotic relatives of schizophrenia patients show that schizotaxia is not merely a theoretical construct but has psychiatric and neurobiological features that justify further research about its nosologic validity (2).

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 have reformulated some aspects of his theory. First, as we describe at greater length in a subsequent section, we have proposed an operational research definition of schizotaxia that allows the concept to be validated or disproved experimentally (4). Second, although Meehl viewed schizotypy as the only clinical phenotype of schizotaxia, we have suggested that schizotaxia produces a stable syndrome of neuropsychological deficits and negative symptoms in most relatives of schizophrenia sufferers (5). Our empirical studies suggest that basic symptoms of schizotaxia are evident in 20% to 50% of first-degree relatives of schizophrenia patients (6,7). In contrast, a much smaller number of such individuals will express schizotypy or schizophrenia. Thus, we view schizotaxia as a broader construct than schizophrenia or SPD. Consistent with this view, only about 10% of relatives will develop psychosis, and less than 10% will develop SPD (8,9). Despite differences with the DSM-IV definition of SPD, we view schizotaxia as a possible form of it. In particular, it is similar conceptually to negative schizotypy, with the addition of neuropsychological deficits. Additional research will be needed to confirm or disprove this view.

A second area of disagreement with Meehl's view involves his suggestion that the etiology of schizotaxia is exclusively genetic. In part because the neurobiological effects of genes cannot always be separated from the neurobiological effects of other adverse environmental variables (for example, pregnancy or delivery complications), we view schizotaxia as the combined effect of both factors. A third area of disagreement involves the nature of the genetic influence in schizophrenia. In 1962, Meehl suggested that schizophrenia resulted from a highly penetrant, dominant gene; however, a more current, consensual view is that most cases of schizophrenia result from the influence of multiple genes of small or moderate effect combined with adverse environmental factors (1,10). Thus, schizotaxia (like schizophrenia) is a genetic disorder in the same sense that diabetes and many other complex conditions are genetic disorders. In these conditions, genetic factors play important, but usually not determining, etiologic roles that interact with environmental factors to produce illness (11). A consequence is that schizotaxia may express itself through various clinical phenotypes, depending on which environmental circumstances and which genes are involved. Consistent with this possibility, studies of nonmedicated, first-degree biological relatives without psychosis show that

they differ from control subjects along multiple clinical, biological, cognitive, and social dimensions of function. Below, we briefly consider several of these.

Clinical Expressions of Schizotaxia

Areas of investigation that have received particular attention in first-degree relatives include psychiatric symptoms, psychophysiological abnormalities, neuroimaging-assessed brain abnormalities, neuropsychological deficits, and psychosocial impairments. The following discussion summarizes representative findings in each domain.

Psychiatric Symptoms

Compared with the general population, nonpsychotic relatives of schizophrenia patients are at high risk for symptoms associated with SPD (9,12,13), although relatives tend to show more negative than positive symptoms. In the Roscommon family study, for example, odd speech, social dysfunction, and negative symptoms strongly discriminated relatives of schizophrenia patients from control subjects, whereas positive symptoms, suspicious behaviour, and avoidant symptoms were less discriminating (14). Moreover, Grove and others showed that relatives have greater deficits on the Physical Anhedonia Scale (which measures negative schizotypal features) than on the Perceptual Aberration Scale (which measures positive schizotypal features) (15), and Tsuang and others reported that negative symptoms (especially flat affect and avolition) were elevated significantly in the schizophrenia families, while positive symptoms were not (16).

Psychophysiological Abnormalities

Psychophysiological abnormalities observed in nonpsychotic relatives of schizophrenia patients include difficulties in smooth-pursuit eye tracking (17,18), prepulse inhibition (19), startle habituation (20), and suppression of auditory-evoked potentials (for example, P50 and P300 waves) (21,22). Although these sensorimotor gating deficits are not specific to schizophrenia (23), they are more prevalent in relatives with schizophrenia spectrum disorders, such as SPD, than they are in control subjects (24–26). Deficits in sensory gating may represent a subset of a broader class of electrophysiological abnormalities in patients with schizophrenia and their relatives. For example, subjects with SPD show abnormal P3 waves over the left temporal lobe (27) and abnormal N400 waves during language-processing tasks (28). It is of particular interest here that sensorimotor (and other electrophysiological) deficits are similar to those observed in schizophrenia patients (21,29–33), and the likelihood of having such abnormalities increases with a greater degree of biological relatedness to a schizophrenia sufferer (for example, [33]). Moreover, these abnormalities are not restricted to relatives with SPD (34). Interestingly, there is long-standing speculation that failures of habituation to sensory stimuli are related both to heightened levels of arousal and to a resultant withdrawal from that arousal (35). These symptoms of withdrawal are consistent with the notion of negative symptoms, which may account in part for the elevated rates of negative symptoms and sensorimotor gating deficits in relatives of schizophrenia patients.

Neuroimaging-Assessed Brain Abnormalities

Numerous studies have demonstrated structural brain abnormalities in schizophrenia (for example, 36). Subjects with schizophrenia spectrum disorders such as SPD, but without psychosis, show similar, though often milder, abnormalities (37,38). Structural magnetic resonance imaging (sMRI) and magnetic resonance spectroscopy studies demonstrate that first-degree relatives of patients with schizophrenia who are not selected for SPD (that is, well over 90%) also differ from control subjects in various ways. For example, such studies demonstrate enlarged third ventricle (39) and pallidal (40) volumes and reduced left amygdala (39), right amygdala, hippocampus, putamen, left thalamus, brainstem (41), cerebellum (40), and overall brain (39) volumes.

Recently, a few studies have focused on the degree of genetic loading for schizophrenia. Lawrie and others compared high-risk subjects (defined as having at least 2 affected first- or second-degree relatives) with first-episode patients and healthy control subjects and found abnormalities that were similar but not identical to those in patients (42). Among these, the relatives showed amygdalo-hippocampal and thalamic regions (bilaterally) that were small, compared with control subjects, but large, compared with patients. Seidman and others compared adult, first-degree relatives without psychosis who had 1 (that is, 'simplex') or 2 (that is, 'multiplex') affected relatives with relatives who had schizophrenia and with normal control subjects (43). Generally consistent with the findings of Lawrie and others, the results showed that within families, nonpsychotic relatives—and particularly those from multiplex families—showed significantly smaller left hippocampi that did not differ from those of patients. Moreover, measures of verbal memory were significantly correlated with left hippocampal volumes.

Another variable related to the degree of risk for schizophrenia involves pregnancy and obstetric complications (44,45). Interestingly, documentation of fetal hypoxia predicted reduced gray matter and increased cerebral spinal fluid in patients and in their nonpsychotic relatives, but not in control subjects (46). These findings underscore the importance of environmental factors in producing not only schizophrenia but also the predisposition to schizophrenia.

In addition to sMRI studies, Seidman and others demonstrated in a functional MRI study that adult nonpsychotic relatives of

schizophrenia patients were significantly impaired on working memory tasks with interference, compared with normal control subjects (47). In both groups, the tasks produced activation in the lateral and medial frontal cortex, posterior parietal and prefrontal cortex, and thalamus. Compared with control subjects, however, the relatives showed a greater number of extraneous, bilateral activations on tasks in which they performed poorly.

Neuropsychological Deficits

As in the domains described above, nonpsychotic relatives of schizophrenia patients demonstrate multiple deficits in cognition that are similar to those seen in schizophrenia sufferers (2,29,48–50). Individuals with SPD, for example, show deficits in nonverbal learning, and especially in verbal learning (51), in working memory (52), and in several executive functions, including concept formation, abstraction, and mental flexibility (53). Similarly, relatives of patients who do not have SPD show dysfunction in several cognitive domains, including motor and perceptual-motor ability, short-term memory, working memory, learning and recall, verbal and language skills, sustained attention, and executive function (2). Several of these deficits coexist in relatives but not in control subjects (54), are stable over a 4-year follow-up period (5), are more prominent in multiplex relatives than in simplex relatives (55), and, when present in childhood (for example, dysfunction in motor skills, verbal memory, and sustained attention), predict schizophrenia-related psychosis in adulthood (56).

Psychosocial Functioning

Poor social functioning is a common finding in child, adolescent, and adult relatives of schizophrenia patients. Compared with control subjects, child relatives demonstrate poor social functioning and restricted interests (57), social incompetence and aggression (58), and shyness, withdrawal, and antisocial behaviour (59,60). In the Danish high-risk study, child relatives were described by teachers as socially isolated, passive, less socially competent, and aggressive; they were described by mothers as both passive and aggressive and by peers as more aggressive, withdrawn, and unlikable (58).

Childhood social deficits increase between childhood and early adolescence and continue through adolescence (61). Results from the Jerusalem Infant Development Study (JIDS) indicate that adolescents who have a parent with schizophrenia show poor social adjustment not related to concurrent onset of schizophrenia (or another disorder) (62). Social difficulties observed in adolescents include increasingly poor functioning at work and at school, a decreased number of friends, immaturity, a lack of popularity with peers, poor peer engagement (especially with members of the opposite sex), and a lack of dating.

Adult relatives without psychosis also demonstrate difficulties in social functioning. Toomey and others showed that relatives of schizophrenia patients exhibit deficits in perception of nonverbal social cues when assessed with the Profile of Nonverbal Sensitivity test (PONS), compared with control subjects, (63).

Taken together, these lines of evidence support the hypothesis that some relatives in schizophrenia families have a clinically meaningful, familiarly transmitted syndrome or set of traits—schizotaxia—that includes negative symptoms, psychophysiological abnormalities, neuroimaging-assessed brain abnormalities, neuropsychological deficits, and psychosocial impairments. While some of these deficits may be present in other schizophrenia-related disorders such as SPD, they also exist independently (see [2] for further discussion of similarities and differences between SPD and schizotaxia).

Definition and Validation of Schizotaxia

The identification of schizotaxic features raises the issue of whether they can be used to select preschizophrenia children for primary prevention protocols. At present, the answer is no. Although, as noted above, studies of children at risk for schizophrenia show that schizotaxia symptoms predict schizophrenia and related disorders (50,56), more work is needed to determine which individuals will or will not develop psychiatric problems. Even less is known about moderating variables that might serve as protective factors to mitigate the effects of vulnerability factors (64). The notion of protective factors is interesting and refers to variables that actively reduce risk, as opposed to the simple absence of variables that confer it. Eventually, an understanding of how risks and protective factors combine to produce an overall level of risk, consistent with a diathesis stress model (1), will be used to tailor individual treatment plans. Until then, we can pursue at least 2 productive lines of inquiry. One of these involves the validation of schizotaxia as a syndrome, and the other involves the schizotaxia intervention protocol to evaluate treatments.

Defining Schizotaxia

The first step is to define a syndrome of schizotaxia. Tsuang and others developed preliminary research criteria for schizotaxia based on a combination of negative symptoms and neuropsychological deficits (4). These criteria reflect only a subset of the symptoms described above. They were selected because evidence for abnormalities in these areas is well established in relatives of schizophrenia patients and because they establish clearly different dimensions to the syndrome. This is particularly important to minimize the likelihood of falsely classifying individuals as schizotaxic (that is, as phenocopies). Nevertheless, the initial criteria are tentative, because schizotaxia is an evolving concept.

In our initial study, subjects who met preinclusion criteria were first-degree relatives of patients with schizophrenia, spoke English as a first language, had estimated IQ scores of at least 70, were aged 19 to 50 years (the age range was partly related to treatment administration), and provided informed consent. Exclusion criteria were designed to minimize the influence of comorbid neurological, psychiatric, or other medical conditions that could mimic schizotaxia symptoms (for example, head injuries, current substance abuse, or history of electroconvulsive treatments). We excluded individuals with any lifetime history of psychosis.

Criteria for schizotaxia were met if a subject was shown to have at least moderately severe negative symptoms and neuropsychological deficits. We used fairly stringent criteria as another hedge against false-positive classification. We assessed negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS) (65). The neuropsychological assessment focused on 3 cognitive domains, including vigilance–working memory, long-term verbal declarative memory, and executive functions. Moderate or greater deficits (defined as approximately 2 or more standard deviations below appropriate norms in 1 domain and at least 1 standard deviation below average in a second domain) were required in at least 2 of the 3 cognitive domains to meet the neuropsychological criteria. In each domain, specific cut-off scores on particular tests were used to assess whether cognitive criteria were met.

Validating Schizotaxic Criteria

The next step is to validate the proposed syndrome or set of traits. Consistent with criteria proposed by Robins and Guze (66), it will be necessary to assess the validity of schizotaxia with converging evidence from multiple domains. In this context, 3 lines of evidence support the validity of the syndrome. First, we recently obtained concurrent validation of schizotaxia by comparing subjects who met our criteria for schizotaxia with those who did not on independent measures of clinical function (67). These measures included the DSM-IV Global Assessment of Functioning Scale (GAF) (68), the Social Adjustment Scale (SAS) (69), the Symptom Checklist-90-R (SCL-90-R) (70), and Chapman's Physical Anhedonia Scale (PAS) (71). On each of these scales, the schizotaxia subjects showed poorer clinical or social function, regardless of whether they were rated by the subjects themselves or by the investigators (blindly). Differences between groups were not attributable to age, IQ, education, parental education, family genetic loading, sex, or comorbid psychiatric disorders. Thus, subjects with schizotaxia as it is currently defined are not impaired globally. Instead, they have clinically meaningful symptoms in circumscribed areas of function.

The second line of support for the validity of schizotaxia involves the response to intervention. If our conceptualization is correct, then treatments that attenuate symptoms in schizophrenia might also attenuate symptoms of schizotaxia. Of the 8 subjects who met our criteria for schizotaxia, 6 agreed to receive a brief 6-week trial of low-dose risperidone (up to 2.0 mg daily) (72). Medication side effects were temporary and mainly mild, and all 6 subjects completed the intervention protocol. Based on subjective assessments, 5 of the 6 individuals reported increased cognitive abilities during the risperidone trial, and 3 reported greater interest in and enjoyment of social activities. Objective assessments demonstrated that 5 out of 6 subjects showed reduced SANS scores, particularly in the Anhedonia Asociality section. Of those 5, 3 showed moderate reductions in their scores (approximately 50%), and 2 showed milder reductions (approximately 25%). Of the 6 subjects, 5 also showed substantial improvements in attention and working memory. On one test of verbal learning and memory, 5 out of 6 subjects showed better learning, although this gain was not reflected on a similar test and was not reflected by better recall over a longer period of time. Overall, these findings are encouraging, although larger, double-blind studies are required to determine whether the initial findings can be replicated.

A third line of support for the validity of schizotaxia involves one component of the syndrome (negative symptoms), because the other component (neuropsychological functioning) was not assessed. We drew a sample from the National Institutes of Mental Health (NIMH) Genetics Initiative for Schizophrenia study (73,74). This multisite collaborative study of the genetics of schizophrenia involved 71 pedigrees that contained 218 nuclear families and 987 individuals. Twenty-nine pedigrees (343 individuals) were of African-American descent, and 42 pedigrees (644 individuals) were of European-American descent. Families were recruited systematically, based upon the DSM-III-R definition of schizophrenia. Each family had 1 member with schizophrenia, and at least 1 other member with either schizophrenia or schizoaffective disorder (depressed type). In our sample, we found that if all subjects with schizophrenia, schizophrenia-related diagnoses (for example, SPD), or other disorders that include psychosis were excluded, at least 1 subgroup remained, characterized by negative symptoms (Stone, Wilcox, Faraone, Tsuang, unpublished). The presence of negative symptoms in a portion of unaffected relatives adds further to the validity of the schizotaxia syndrome, as currently defined.

The Schizotaxia Intervention Protocol

Even with a working research definition of schizotaxia and preliminary evidence of its validity, the field is not ready for prevention trials. As noted above, we are not yet able to

identify with acceptable levels of certainty who will and will not develop schizophrenia. However, our current knowledge about schizotaxia does suggest a method for evaluating treatments that may someday be useful for preventing schizophrenia. The method, called the "schizotaxia intervention protocol," is straightforward: among schizophrenia patients, select a sample of first-degree relatives with schizotaxia. Then, using standard clinical trial protocols, determine whether a putative preventive intervention modifies symptoms of schizotaxia in an acute trial. The underlying assumption is that any intervention which attenuates a feature of schizotaxia is a reasonable candidate for a prevention trial, when such trials become feasible.

The notion that schizotaxia symptoms or traits observed in first-degree relatives share etiologic and pathophysiological pathways with schizophrenia was central to our hypothesis that low dosages of risperidone would attenuate such symptoms, as described above. In that study, we administered the treatment to adults aged 30 to 49 years. Their risk for developing schizophrenia was thus statistically lower than when they were younger, although it still exceeded that of the general population. The same reasoning that underlies treatment of schizotaxia for its own sake (that is, to reduce symptoms in affected individuals who might not otherwise receive treatment) underlies its utility in prevention strategies. If adult first-degree relatives share etiologic and pathophysiological elements with their ill relatives, it follows that the ill relatives share such elements with subjects who may be regarded as preschizophrenic. If this is true, then any intervention that seeks to mitigate these elements (that is, schizotaxia symptoms or the function of their underlying neurobiological substrates) might also work to reduce the likelihood of psychosis. Further, this assumption is reasonable because first-degree relatives of patients with schizophrenia show an elevated risk for carrying schizophrenia susceptibility genes (1), and features of schizotaxia observed among adult relatives are similar to those seen in children who eventually develop schizophrenia (2).

The schizotaxia intervention protocol has several major advantages. One is that it is applicable to a wide range of potential interventions. While the use of medications is particularly likely to receive attention, other modalities, such as psychotherapy, psychosocial treatments (for example, [2,75]), or combinations of treatments, may be at least as useful. Another major advantage of the schizotaxia intervention protocol is that it can avoid some of the ethical issues raised by primary prevention studies in schizophrenia. In particular, prevention studies with children and adolescents have the unintended effect of labelling them as future schizophrenia patients. This raises the very real possibility of stigmatization and emotional harm to the subjects and to their families. Moreover, the type of medications likely to be used in prevention trials may pose greater risks to children and adolescents than to adults. The use of antipsychotic medications to treat children, for example, has been limited in part because of concerns about side effects (76). Both considerations (that is, concerns about stigmatization and about medication effects) preclude their use without solid evidence of their efficacy, but even nonpharmacologic interventions can be psychologically harmful if their use is not predicated on a solid rationale. Schizotaxia, by contrast, can be defined in adult relatives of patients with schizophrenia, and putative preventive interventions can be evaluated without the use of children or adolescents.

Eventually, if schizotaxia is validated in adults, if successful remediation of schizotaxic symptoms or traits is demonstrated, and if a homogeneous target population is accurately defined, then interventions at earlier ages may be considered. Presumably, trials with older adolescents would precede trials with younger age groups. The end point would involve trials with preprodromal, prepsychotic samples. At present, the focus is likely to remain on adults. Although our study of risperidone in relatives of patients with schizophrenia is an encouraging initial application of the schizotaxia intervention protocol (in addition to the evidence it provides for the validation of the syndrome) (72), larger studies, double-blind protocols, and additional treatments are needed to clarify the extent to which symptoms of schizotaxia are reversible.

Present and Future Directions

While the concept of a predisposition to schizophrenia has intrigued researchers for close to 100 years, its study is more recent. Four decades of research, however, have established schizotaxia as a clinically meaningful condition (2). One of the most significant aspects of research with relatives of schizophrenia patients involves the nature of schizotaxia symptoms. It is clear from high-risk longitudinal studies, from family studies of cognitive function, and from studies of neuroimaging, neurochemistry, psychophysiology, and social functioning (22,43,48,56,63,77), that the predisposition to develop schizophrenia involves more than the clinical symptoms required for a DSM or ICD diagnosis of the disorder. As we proposed recently, the clinical symptoms required for a diagnosis emphasize the role of psychosis and may reflect a relatively nonspecific end state of the effects of schizotaxia plus psychosis (78). In contrast, many of the features of schizotaxia may be closer to the genetic and other adverse etiologic factors that produce the predisposition to schizophrenia. Consequently, symptoms of schizotaxia may come to represent particularly promising treatment targets for prevention protocols. These points do not detract from the major achievements and utility of the DSM and ICD systems in advancing psychiatric diagnosis, especially in reliability but also in

validity. Rather, they suggest possible pathways for continued progress in confirming the reliability and validity of psychiatric classification.

At this point, a reasonable strategy is to proceed on the 2 parallel fronts described above. First, there is a clear need to continue to validate schizotaxia as a syndrome or set of traits. Although we do not suggest that our conception of the predisposition to develop schizophrenia is the only one possible, it is a promising one that merits additional investigation. Whether our conception or another one is used, a working model is needed to address the existence of a syndrome that has a biological connection to schizophrenia and to address its relation to the nonspecificity of psychosis. To some extent, the emergence of a more unified model of schizotaxia (that is, one that is likely to include most of the major themes of schizotaxia research) is mainly a matter of time. For example, if the current components of the schizotaxia syndrome are validated (that is, negative symptoms and neuropsychological deficits), the concept will certainly evolve to encompass additional dimensions of schizotaxic features (for example, neuroanatomical, neurochemical, neuroendocrine, psychophysiological, social, and other clinical components). As it evolves, an understanding of the interrelations among these dimensions will provide an increasingly integrated view of the predisposition to develop schizophrenia.

The second line of research is related to the first and involves the continued use of the schizotaxia intervention protocol to develop methods to reduce schizotaxia symptoms. Progress in each of these areas will spur progress in the other. As the identification and validation of schizotaxic features progresses, clearer treatment targets will become available. Similarly, as the field develops interventions to reduce symptoms, the pressure to define a syndrome of predisposition will become more acute. Hopefully, each of these lines of research will aid the development of interventions to prevent psychosis in people with schizotaxia.

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Résumé : Comprendre la prédisposition à la schizophrénie : vers l'intervention et la prévention

Objectif : L'intervention précoce en vue de prévenir la schizophrénie est un des buts les plus importants de la recherche sur la schizophrénie. Cependant, le domaine n'est pas encore prêt à entamer des essais pour prévenir les symptômes avant-coureurs ou psychotiques chez les personnes qui sont à risque de développer la maladie. Dans cet article, nous abordons certains des obstacles majeurs qu'il faut examiner avant de pouvoir mettre en oeuvre les stratégies de prévention.

Méthode et résultats : L'un des obstacles les plus importants est l'identification d'un syndrome ou d'un ensemble de traits qui reflètent une prédisposition à la schizophrénie et qui peuvent fournir des cibles d'intervention éventuelles. Dans une récente reformulation du concept de la schizotaxie de Paul Meehl, nous intégrons les résultats de la recherche obtenus au cours des 40 dernières années pour proposer un syndrome ayant des manifestations cliniques significatives. Nous examinons la conceptualisation de ce syndrome ainsi que son expression clinique multidimensionnelle. Nous décrivons ensuite les critères diagnostiques de la recherche préliminaire qui seront utilisés chez les parents du premier degré, adultes et non psychotiques des patients diagnostiqués à l'aide des critères de la schizophrénie, selon les symptômes négatifs et les déficits neuropsychologiques. Font suite des données probantes à l'appui de la validité du syndrome proposé, qui inclut principalement la dysfonction sociale et la réaction à une faible dose des nouveaux antipsychotiques.

Conclusions : Les progrès constants vers une application éventuelle de stratégies de prévention de la schizophrénie feront appel à des efforts soutenus en vue de valider les traits qui reflètent une prédisposition au risque de développer la maladie (par exemple, la schizotaxie), à des études de suivi pour confirmer les résultats originaux et à la définition d'interventions préventives potentiellement utiles.