“Schizotaxia”: Clinical Implications and New Directions for Research

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Abstract

We sought to show that (1) schizotaxia (Meehl’s term for the predisposition to schizophrenia) is a clinically consequential condition, and (2) distinguishing it from schizotypal personality disorder may be useful from both clinical and scientific perspectives. We review the features of schizotaxia that may be relevant in clinical settings and discuss their implications for the diagnosis, psychosocial functioning, family intervention and treatment of people in schizophrenia families. Our review indicates that prior work finds some of the nonpsychotic and nonschizotypal relatives of schizophrenia patients to have a psychiatric syndrome characterized by negative symptoms, neuropsychological impairment, and psychosocial dysfunction. Following Meehl, we call this constellation of clinical and neurobiological features schizotaxia. The studies we review suggest it may be worthwhile to consider schizotaxia as a separate diagnostic class. Doing so would alert clinicians to a neurobehavioral syndrome not adequately covered by current diagnostic criteria and would motivate researchers to develop diagnostic and therapeutic approaches aimed at helping schizotaxic individuals and, perhaps, preventing the onset of schizophrenia.

Keywords: Schizophrenia, schizotaxia, genetics, prevention, spectrum

the clinical features of schizotypia and to motivate researchers to develop diagnostic and therapeutic approaches aimed at helping those with schizotypia.

Clinical Features of Schizotypia

The clinical descriptions of most psychiatric conditions originally derived from reports of patients who presented with a specified cluster of signs and symptoms. In contrast, clinical descriptions of schizotypia come from studies of people genetically predisposed to schizophrenia: the relatives of schizophrenia patients. Such studies infer a clinical or neurobiological abnormality to be a potential feature of schizotypia if it is elevated among these relatives and among schizophrenia patients. In this section we consider three clinically relevant areas of research: psychiatric signs and symptoms, neuropsychological performance, and psychosocial functioning.

Psychiatric Signs and Symptoms. Because family, adoption, and twin studies firmly support the idea that relatives of schizophrenia patients are at high risk for schizotypal personality disorder (Torgersen 1985; McGuffin and Thapar 1992; Battaglia and Torgersen 1996), several studies have attempted to determine which schizotypal symptoms are most common among the relatives of patients with schizophrenia. For example, Gunderson et al. (1983) found that relatives of schizophrenia patients were at high risk for social isolation, interpersonal dysfunction, and impoverished affective experiences. In that study, mild psychotic like symptoms such as recurrent illusions and magical thinking were more common in relatives who were themselves diagnosed with borderline personality disorder. Tsuang et al. (1991) reported that negative symptoms (especially flat affect and avolition) were significantly elevated in the schizophrenia families, while positive symptoms were not. In the Roscommon family study, odd speech, social dysfunction, and negative symptoms strongly discriminated relatives of schizophrenia patients from controls. In contrast, positive symptoms, suspicious behavior, and avoidant symptoms were less discriminating (Kendler et al. 1995).

Consistent with these studies, psychometric assessments of schizotypal symptoms among relatives of patients with schizophrenia have found a predominance of negative rather than positive symptoms. For example, Grove et al. (1991) showed that relatives of schizophrenia patients have greater deficits on the Physical Anhedonia Scale (which measures negative schizotypal features) than on the Perceptual Aberration Scale (which measures positive schizotypal features). Although we must consider the possibility that artifacts of self-report scales such as defensiveness might have led to these results, their consistency with direct interview studies is compelling.

In summary, the literature to date provides firm support for the idea that nonpsychotic relatives of schizophrenia patients are at risk for schizotypal personality traits. The literature also shows that the relatives in schizophrenia families are more likely to express negative symptoms than positive symptoms, although, as the Roscommon study showed, positive schizotypal symptoms are also found among nonpsychotic relatives of schizophrenia patients.

These studies have focused on positive and negative schizotypal traits because several studies suggested that schizotypal symptoms fell along two dimensions: cognitive-perceptual and interpersonal, or positive and negative (Raine and Allbutt 1989; Kendler et al. 1991). But three- and even four-dimensional solutions have also been reported by others (Muntaner et al. 1988; Bentall et al. 1989; Hewitt and Claridge 1989; Raine et al. 1994; Chen et al. in press). These studies suggest that, as is the case for schizophrenia, we may need a third dimension, disorganization, to adequately describe schizotypal signs and symptoms. Thus, a more complex view of clinical schizotypal traits should be examined in future studies of schizotypia.

Given that negative schizotypal symptoms are prominent among relatives of schizophrenia patients, we would expect these relatives to also show an excess of schizoid personality disorder. But relevant data are mixed. In a Danish adoption study, the biological relatives of schizophrenia patients did not show an excess of schizoid personality (Kety et al. 1994). Similar results were reported in a family study by Maier et al. (1994a; 1994b) and a twin study by Torgersen et al. (1993). In contrast, two family studies found higher rates of schizoid personality among relatives of schizophrenia patients compared with relatives of controls (Dorfman et al. 1993; Kendler et al. 1993). Because there are no systematic differences between studies that do and do not find schizoid personality in schizophrenia families, further work is needed to clarify the nature of the negative symptoms of schizotypia and to determine why these are expressed in negative schizotypal, but not schizoid traits.

Neuropsychological Performance. When the genes for schizophrenia do not lead to frank psychosis, will they nonetheless affect the brain and lead to neurobiological abnormalities and neuropsychological deficits? Several decades of research suggest that the answer is "yes" (Seidman 1997). Abnormalities found among relatives of schizophrenia 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), neuropsychological impairment (Kremen et al. 1994), and structural brain abnormalities assessed by magnetic resonance imaging (Seidman et al. 1997). Although each of these domains of research has provided valuable data about the neurobiological features of schizotaxia, we focus here on the neuropsychological findings because they describe deficits that have clinically meaningful implications for members of schizophrenia families.

Two research paradigms—studies of children of schizophrenia patients and studies of adult relatives of schizophrenia patients—have provided data about the neuropsychological features of schizotaxia. It is useful to distinguish studies of child and adult relatives because, unlike children, adults have lived through some, or all, of the risk period for schizophrenia. Thus, both types of relative groups will include some schizotaxic individuals but studies of children are more likely to include cases that will eventually develop schizophrenia.

One neuropsychological function that differentiates child relatives is motor ability. Impaired motor ability presents in children as soft neurological signs such as disturbed gait, poor balance, uncoordinated motor incoordination and impaired mirror drawing (Lifshitz et al. 1985; Asarnow and Goldstein 1986). In contrast, motor functioning has been less consistently impaired among adult relatives of schizophrenia patients (Kinney et al. 1986; Cannon et al. 1994; Faraone et al. 1995b; Kinney et al. 1991; Rosen et al. 1991).

Perceptual-motor speed tests assess the ability to perceive stimuli and react to them quickly in an appropriate manner. Among the children of schizophrenia patients, there is consistent evidence for deficits on such tests (Erlenmeyer-Kimling et al. 1982; Nuechterlein and Dawson 1984). Similar results have also been found among adult relatives. For example, in studies from two different research groups, nonpsychotic relatives were significantly slower on the Trail Making Test (Pogue-Geile et al. 1991; Keefe et al. 1992; Keefe et al. 1994). Similar trends were reported by others (Goldberg et al. 1990; Condray and Steinhauser 1992).

Tests of short-term memory assess the ability to retain information in memory for a brief duration (e.g., recalling a phone number after finding it in the directory). In most (Mednick and Schulsinger 1968; Sohlberg 1985; Landau et al. 1989) but not all (Worland and Hesselbrock 1980) studies, children of schizophrenia patients showed poor short-term memory as measured by oral arithmetic scores (which require short-term memory to manipulate mathematical concepts). They are not consistently impaired when asked to recall a string of digits (Mednick and Schulsinger 1968; Worland and Hesselbrock 1980; Cornblatt and Erlenmeyer-Kimling 1985; Lifshitz et al. 1985), but they do show deficits if distracted during digit recall (Harvey et al. 1981; Winters et al. 1981; Cornblatt and Erlenmeyer-Kimling 1985; Spring 1985). Short-term digit recall has not been impaired in studies of adult relatives (Roxborough et al. 1993; Faraone et al. 1995b), probably because of the lack of a distraction component in those studies.

Impaired vigilance (often referred to as sustained attention) is usually measured with a continuous performance test (CPT), which presents a long series of stimuli and asks the subject to respond whenever a rare target stimulus appears. Cornblatt and Keilp's (1994) review of 40 studies using the CPT shows that vigilance deficits are evident among both the adult and child relatives of schizophrenia patients.

There has been little neuropsychological evaluation of verbal ability and language among children of schizophrenia patients. Most studies of adult relatives have not found differences in general verbal ability, although there was some evidence for poorer vocabulary scores in one sample (Faraone et al. 1995b). Notably, three studies found significant impairments in speed and ease of verbal production (Pogue-Geile et al. 1991; Keefe et al. 1992; Roxborough et al. 1993; Keefe et al. 1994) and Cannon et al. (1994) found deficits in language abilities.

Difficulties with language have also been documented in studies of communication deviation, which have found unclear, amorphous, disruptive, or fragmented communication among the parents of schizophrenia patients (Wynne and Singer 1963b; Singer and Wynne 1965; Doane et al. 1981; Rund 1986; Velligan et al. 1990; Docherty 1993; Docherty 1994; Miklowitz 1994; Rund 1994; Velligan et al. 1995; Docherty et al. 1996; Velligan et al. 1996). Given these communication problems, it is not surprising that relatives of schizophrenia patients also show signs of thought disorder (Lidz et al. 1962; Wynne and Singer 1963a; Wynne and Singer 1963b; Rosman et al. 1964; Singer and Wynne 1965; Schopler and Loftin 1969; Arboleda and Holzman 1985; Saccuzzo et al. 1988; McConaghy 1989; Shenton et al. 1989; Romney 1990). Indeed, communication deviance and thought disorder are usually associated with one another (Docherty 1994). The thought disorder observed among relatives is never as severe as that seen among schizophrenia patients, but it does share qualitatively similar characteristics such as looseness of associations, autistic logic, word finding difficulties, perseveration, and conceptual disorganization.

Studies of children of schizophrenia patients have provided scant information about the ability to learn and recall verbal material. Adult relatives, however, have difficulties recalling the details of a short story (Roxborough et al. 1993; Cannon et al. 1994; Faraone et al. 1995b; Faraone et al. in press;) or using the semantic similarities
of words to aid in their recall (Lyons et al. 1995). In contrast, deficits in simple visual-spatial learning and memory tasks are not usually found in schizotaxic adults (Orvaschel et al. 1979; Driscoll 1984; Neuchterlein and Dawson 1984; Cannon et al. 1994), although some positive findings have been reported (Faraone et al. 1995b; Faraone et al., in press).

Executive functions are essential for planning, for processing abstract concepts and for using retained information in other cognitive tasks. Children of people with schizophrenia do poorly on measures of concept formation (Asarnow et al. 1978) but not on object sorting tests that require them to abstract a rule from a series of stimulus presentations (Winters et al. 1981). Adult relatives also do poorly on concept formation tests (Pogue-Geile et al. 1989; Condray and Steinhauser 1992) and, although there is some contrary evidence (Condray and Steinhauser 1992; Keefe et al. 1992; Roxborough et al. 1993; Keefe et al. 1994), most studies have found adult relatives to be impaired on sorting tests (Pogue-Geile et al. 1991; Franke et al. 1992; Mirsky et al. 1992; Faraone et al. 1995b). Consistent with these findings of executive dysfunction, adult relatives are impaired on tests of working memory that assess the ability to remember information over a short period of time so that it can be used in a subsequent task (Park et al. 1995; Faraone et al. in press).

Table 1 summarizes the neuropsychological studies of child and adult relatives. It renders a clear conclusion: in schizophrenia families, some relatives have neuropsychological deficits in multiple domains. The domains impaired in these relatives are consistent with the cognitive dysfunctions thought to be central to schizophrenia patients themselves. This consistency supports the idea that some relatives in schizophrenia families have a familially transmitted syndrome—schizotaxia, which manifests as abnormalities in neuropsychological performance.

**Psychosocial Functioning.** If schizotaxia is a clinically significant condition, it should be associated with disability at work, in school, or with interpersonal relationships. For adult relatives, one might infer such disability from their profile of neuropsychological impairments. For example, at work and in school, impaired executive functions will jeopardize successful achievement, which requires planning and organizational skills and the ability to process abstract concepts. Moreover, impairments in vigilance will make it difficult for schizotaxic people to succeed in settings that require concentration over long periods. One might infer interpersonal dysfunction from the subtle thought disorder and communication associated with schizotaxia.

Although these neuropsychological inferences are compelling, few studies of adult relatives have directly examined psychosocial functioning. One exception is the work of Toomey et al. (1997), who reported adult relatives to have deficits in the social perception of nonverbal cues; these deficits were associated with poor vigilance. We also know that schizotaxia leads to negative symptoms, which include indexes of psychosocial failure such as impersistence at school or work, recreational interests and activities, sexual activity, and relationships with friends and peers.

In contrast to the dearth of psychosocial information about adult relatives, psychosocial dysfunction has been documented among the children of schizophrenia patients ("child relatives" for short). For example, data from the New York High-Risk Project found child relatives to have poorer social functioning and more restricted interests

<table>
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<tr>
<th>Neuropsychological domain</th>
<th>Children/adolescents</th>
<th>Adults</th>
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<tr>
<td>Motor ability</td>
<td>+</td>
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<td>Perceptual-motor speed</td>
<td>+</td>
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<td>Short-term memory</td>
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<td>Sustained attention</td>
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<td>Verbal ability and language</td>
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<td>Verbal learning and memory</td>
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<td>Visual-spatial learning and memory</td>
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<td>+/-</td>
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<td>Executive functions</td>
<td>+</td>
<td>+/-</td>
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**Note.** + = impaired; − = not impaired; +/- = variable results; ? = not sufficiently studied.
than psychiatric or normal controls (Small 1990). The social competence of child relatives decreased between childhood and early adolescence but remained stable from early to late adolescence (Dworkin et al. 1994).

In the Israeli high risk study, Auerbach et al. (1993) found boys of schizophrenia parents to be more withdrawn than boys of nonschizophrenia parents. The boys who developed schizophrenia-related disorders had been shy and withdrawn or aggressive and antisocial (Hans et al. 1992). In the Danish high risk study, child relatives were described by teachers as passive and socially isolated, and by mothers as both passive and aggressive. When compared with controls, teachers described child relatives as less socially competent and more aggressive; peers described them as more aggressive, withdrawn, and unlikable (Ledingham 1990). Notably, Asarnow's review (1988) determined that all studies of adolescent relatives have found them to have significant social dysfunction.

Thus, like neuropsychological impairment, there is consistent evidence for psychosocial dysfunction among children at risk for schizophrenia. Moreover, studies of children link these two domains of dysfunction. For example, in Auerbach et al.'s (1993) study, the socially withdrawn children also had motor abnormalities. Walker and Lewine (1990) rated videotapes of children who subsequently developed schizophrenia. These children had neuropsychological impairments (poor fine and gross motor coordination) and evidence of social dysfunction (poor eye contact, more negative affect and low social responsivenes). In the New York High-Risk Project, attentional problems in childhood predicted social dysfunction in adolescence and social isolation in adulthood (Dworkin et al. 1993). Notably, an association between neuropsychological performance and functional impairment is also seen for schizophrenia patients (Green 1996).

Because neuropsychological impairment is evident at an early age (e.g., Fish and Hagin 1973) and typically emerges prior to social dysfunction (Dworkin et al. 1993), it is intriguing to speculate about a causal link between these two features of schizotaxia. As suggested by Correll and Keilp (1994), an early attentional deficit could impair the processing of interpersonal information and lead to failure in social interactions.

Correll and Keilp's model predicts that interpersonal interactions will frequently fail, leading to increased stress and a repeated cycle of increased psychosocial difficulties and stress. We would extend this model to include other neuropsychological deficits as potential causes of psychosocial dysfunction. Future confirmation of these causal links would suggest that treatment of neuropsychological deficits might improve the psychosocial functioning of schizotaxic people.

Clinical Implications of Schizotaxia

To recap, schizotaxia is a subtle syndrome of brain dysfunction expressed, in part, as negative symptoms and neuropsychological deficits, but not as psychosis. This syndrome is qualitatively similar—yet less severe—than that observed among schizophrenia patients. In this section we address questions that these findings pose for clinical practice: How does one diagnose schizotaxia and differentiate it from schizotypal personality? Does schizotaxia have implications for family interventions for schizophrenia? What are the treatment options for schizotaxic people?

How Does One Diagnose Schizotaxia and Differentiate It From Schizotypal Personality? For schizotaxia to be a useful diagnostic class, requires the formulation of specific diagnostic criteria is required. But specifying diagnostic criteria is not currently possible given that this issue has not been directly examined in prior research. We expect such criteria to evolve as future research assesses the concurrent and predictive validity of schizotaxia criterion sets. Moreover, such research will need to document the divergent validity of schizotaxia: Is the syndrome sufficiently different from other disorders to warrant a separate category? Here we address the most difficult differential diagnostic hurdle for schizotaxia: is it sufficiently different from schizotypal personality to warrant a separate category?

Notably, in a reformulation of his theory, Meehl (1989) conceded the possibility that some schizotaxic persons might not develop schizotypal personality. Although he thought this outcome would require “a sufficiently well-managed prophylaxis” (p. 938), subsequent data have shown that—even without intervention—many schizotaxic persons will neither become schizotypal nor develop schizophrenia. The core features of schizotaxia (negative symptoms and neuropsychological impairments) occur in 20 percent to 50 percent of such relatives (Faraone et al. 1995a, 1995b), but less than 10 percent of adult family members of schizophrenia patients will be diagnosed with schizotypal personality disorder. Thus, unlike schizotypal personality, schizotaxia appears to be common among relatives of schizophrenia patients. Because schizotypal personality should be evident by adulthood, finding that many schizotaxic adults are not schizotypal shows that the former condition does not always evolve into the latter.

There is another reason to demarcate schizotaxia from schizotypal personality: The latter is a heteroge-
neous disorder. This heterogeneity stems from the two methods used to study it: The "clinical method" has identified personality disordered patients who seem to exhibit a mild form of schizophrenia symptoms; the "family research method" has identified relatives of patients with schizophrenia who exhibited subtle schizophrenia-like psychopathology (Kendler 1985). Although the people recruited by these two methods show some clinical similarities, several studies suggest that "clinical" and "familial" schizotypal personality may be different disorders (Kendler 1985).

For example, among subjects diagnosed with schizotypal personality, Torgersen (1985) reported that the negative symptoms of social withdrawal and impairment were genetically related to schizophrenia while positive, psychotic-like symptoms were not. Thaker et al. (1993a) found clinical schizotypal subjects to show more evidence of magical ideation and perceptual ideation than familial schizotypal subjects. The two groups, however, did not differ in either physical or social anhedonia.

A family study reported elevated rates of schizotypal personality among relatives of patients with mood disorder (Squires-Wheeler et al. 1989), but compared with schizotypal relatives in schizophrenia families, the schizotypal relatives in mood-disordered families were more likely to show symptoms of anxiety and depression at a follow up assessment (Squires-Wheeler et al. 1992). Similarly, Lyons et al. (1994) compared schizotypal relatives of schizophrenia probands with schizotypal relatives of mood disordered probands. The former group had more inadequate rapport and anxiety whereas the latter had higher rates of impulsive-dramatic personality disorders.

Biological studies also find evidence for two types of schizotypal personality. An early review by Siever (1985) concluded that a subgroup of schizotypal subjects exhibited biological abnormalities that were similar to those seen in schizophrenia patients. This subgroup manifested negative symptoms and neuropsychological impairment (two features of schizotaxia), but rarely exhibited positive symptoms. Moreover, Condray and Steinhauer (1992) found impaired language comprehension among schizotypal subjects with a family history of schizophrenia, but not among those without such a history and Kendler et al. (1991) showed that among schizotypal subjects, negative symptoms predicted attentional and eye-tracking dysfunction (likely features of schizotaxia) but the positive syndrome did not. Results consistent with these were reported by Thaker et al. (1996), who assessed eye tracking among subjects with paranoid, schizoid, and schizotypal personality. Eye-tracking abnormalities were associated with these disorders, but only for subjects with a family history of schizophrenia.

The view that schizotypal personality is heterogeneous finds further support from family studies. For example, Thaker et al.'s review (1993a), shows that most studies of clinically derived schizotypal probands did not find elevated rates of schizophrenia among the proband relatives. Subsequent reports have also supported that assertion (Battaglia et al. 1995). These findings suggest that many clinically ascertained schizotypal patients do not carry the genetic predisposition to schizophrenia (i.e., they do not have schizotaxia).

In figure 1, schizotaxia (the left circle) and schizotypal personality (the right circle) are shown as conditions that sometime co-occur. The lack of complete overlap between the two circles illustrates the notion that schizotaxia is a broader construct than the subset of schizotypal persons who have predominantly negative symptoms. The area of overlap between the circles corresponds to people showing both schizotaxic and schizotypal symptoms. These people have been described as having "familial" schizotypal personality in the research literature. The portion of the schizotypal personality circle not overlapping with the schizotaxia circle contains those patients described as having "clinical" schizotypal personality.

We leave to future research the goal of parsing the comorbidity between schizotypal personality and schizotaxia. Because comorbidity is a common feature of psychiatric illness, recognizing both conditions and their comorbidity might be a reasonable solution. In contrast, it may be preferable to sharpen diagnostic criteria with the goal of separating schizotaxia from schizotypal personal-

![Figure 1. Overlap between schizotaxia and schizotypal personality](https://academic.oup.com/schizophreniabulletin/article-abstract/27/1/1/1828892/128882?download=true)
ity. This would require psychometric studies that would find diagnostic criterion sets that eliminate the extensive comorbidity between the two conditions.

If successful, such studies would designate schizotaxia as the syndrome of negative symptoms and neuropsychological dysfunction observed among relatives of schizophrenia patients (all of figure 1’s schizotaxia circle) and schizotypal personality disorder as the schizotypal-like syndrome in which positive symptoms dominate the clinical picture (the portion of figure 1’s schizotypal personality circle that does not overlap with the schizotaxia circle). Reformulating the diagnoses in this manner would increase the homogeneity of schizotypal personality and free researchers to define schizotaxia in a manner that might further validate it as a syndrome.

If future work refines definitions of schizotaxia and schizotypal personality, it will also need to clarify how these conditions are related to schizophrenia, which is itself clinically and genetically heterogeneous (Tsuang and Faraone 1995). Such work would need to consider alternative theoretical models. For example, there may be several dimensions of schizotypia and schizotypal personality. Predisposing a person to each of these may be different sets of genes that, in combination, predispose a person to schizophrenia. It is also possible that the genes predisposing people to schizotypia and schizotypal personality may be related to different forms of schizophrenia. Moreover, it is not clear if schizotypia is a discrete entity or a quantitative trait that varies in severity from subclinical to clinically meaningful manifestations. Addressing such issues could facilitate genetic studies, and might clarify the treatment implications of schizotypia for people in schizophrenia families.

**Does Schizotaxia Have Implications for Family Interventions for Schizophrenia?** Because families are often involved in treatment programs for patients with schizophrenia, it is likely that many schizotypic persons participate in the treatment of their relative with schizophrenia. Psychoeducational family therapies ask family members to learn facts about the disorder and methods of coping with their relative’s illness (Falloon et al. 1986). Moreover, response acquisition methods are often used to teach communication skills to family members (Falloon et al. 1986). Because family members need to learn, recall, and generalize the use of these skills, therapists engage family members in a variety of tasks requiring intact neuropsychological functioning.

Although the nonschizotypic relatives should benefit from family interventions, it is likely that the neuropsychological impairments of other family members would hinder the course of treatment (Seidman 1994). The distractibility of schizotypic relatives may make it difficult for them to follow lessons and absorb information. Memory deficits will likely compromise their ability to learn skills and use them outside the treatment session. Relatives with abstraction deficits will not be able to integrate course material and plan for its use in the home environment. Considering that family interventions also tax the capacity of family members to tolerate difficult emotions and face family conflict, the added burden of neuropsychological deficits may make it hard for family members to learn skills or to generalize them from treatment sessions to real-world settings.

Thus, full participation in family interventions will likely be compromised by the neuropsychological impairments of schizotypia. Moreover, it is possible that therapist observations of inattentiveness, slow learning, or poor memory for lessons may be misinterpreted as indicating resistance on the part of the family member. That could lead to counterproductive therapeutic strategies.

**What Are the Treatment Options for Schizotaxia?** The features of schizotaxia raise two distinct questions for treatment. First, can we alleviate the negative symptoms, neuropsychological impairment, and social dysfunction of adult schizotaxia? Second, can we prevent schizophrenia in schizotypic adolescents?

**Treating adult schizotaxia.** Age-at-onset data show that the risk for schizophrenia becomes very small in the third decade of life (Pulver et al. 1990; Faraone et al. 1994; Sham et al. 1994). Moreover, most patients with schizotypal personality disorder do not go on to develop schizophrenia. Thus, most adults with schizotypia are not at high risk for schizophrenia and any proposed treatment of such adults cannot be predicated on the notion that it will prevent that disorder. Instead, proposed treatments should be aimed at alleviating the negative symptoms, neuropsychological impairment, and social dysfunction of schizotaxia.

Clinicians who work with schizophrenia families frequently deal with psychologically distressed or psychologically impaired relatives. When clinicians interpret distress as a reasonable reaction to the schizophrenia in the family, they will try to help family members cope with the relative’s illness. Such interventions can be very effective, but they do not address an alternative clinical hypothesis: that some of the distress and social disability of family members might be a direct effect of schizotypia.

Moreover, the psychological vulnerabilities of schizotypic people may be exacerbated by stress, which would include the emotional burdens and practical complexities of dealing with a relative with schizophrenia along with the background level of life events and psychosocial conflict that would occur in a nonschizophrenia family. These considerations suggest that the direct treatment of schizotypia might be useful in the therapeutic approach to schizophrenia families. But, how would one...
treat schizotaxia? Although there is no specific therapy for the condition, here we speculate on potential psychological and pharmacological approaches, which may not be mutually exclusive.

The treatment of schizotaxia may benefit from methods effective in the psychotherapy of other neurodevelopmental conditions (e.g., adult attention deficit hyperactivity disorder), which share some clinical features with schizotaxia. As discussed by Seidman (1994), therapists who treat patients with subtle neuropsychological impairments should attend to several issues.

First, the therapist should have an objective understanding of the patient's neuropsychological strengths and weaknesses. This knowledge helps patients and the significant people in their lives to reformulate their view of the behavioral consequences of cognitive dysfunction. For example, schizotaxic people with deficits in attention and verbal memory may view themselves as "stupid" because they cannot learn in the many educational settings that require these skills. Therapy can help them reinterpret these difficulties and develop coping strategies. Moreover, teaching schizotaxic people about their neuropsychological profile might help them develop realistic expectations and better plan their occupational and educational pursuits.

Clinicians could also help schizotaxic people develop cognitive-behavioral strategies to cope with specific deficits. For example, relatives with memory deficits would benefit from learning mnemonic strategies; those with abstraction deficits could be taught systematic methods of planning and organizing their activities. Thus, standard tools used to aid recall (e.g., appointment books, calendars) could be part of the therapeutic toolbox.

Therapists can also use neuropsychological information to facilitate an empathic approach to the issues of shame, inferiority, and performance anxiety that often arise in patients with neurocognitive disorders (Seidman 1994). Such maladaptive emotions may stem directly from the experiences of failure caused by the schizotaxic, neuropsychological syndrome. They may be reactions to the stress and stigma of having a relative with schizophrenia. Furthermore, the language and self-regulation deficits of schizotaxic people may make it difficult for them to articulate their awareness of these feelings. Without therapeutic attention, these emotional consequences might worsen cognitive performance and lead to a downward spiral toward further dysfunction.

Although psychological interventions, as noted above, would appear to be appropriate, research is needed to clarify which psychotherapeutic approaches are most effective and whether pharmacotherapy would also be useful. Of course, there are no known medications for schizotaxia, and no clinical guidelines can be suggested at this time. It is worthwhile, however, to examine the implications for future pharmacotherapeutic research suggested by the data reviewed in this article. These data suggest that schizotaxia shares causal and pathophysiological components with schizophrenia. Thus, the data raise a provocative question: Would schizotaxic traits respond to medications used in the treatment of schizophrenia?

Answering this question is not straightforward. The answer must assume that antipsychotic medications are of value in treating negative symptoms and improving neuropsychological functions. Although treatment with low doses of typical neuroleptic drugs has shown some efficacy for schizotypal personality (e.g., Hymowitz et al. 1986), these drugs may not effectively treat the schizotypic syndrome of negative symptoms and neuropsychological impairment. Moreover, studies of schizotypal patients suggest that neuroleptic side effects lead to medication discontinuation rates as high as 50 percent (Hymowitz et al. 1986).

The atypical or novel antipsychotic drugs may be more promising for the treatment of schizotaxia. Although not all studies agree, and the relative effects of these agents on "primary" and "secondary" symptoms is under debate (Carpenter et al. 1995; Meltzer 1995), several reports suggest that the first of the atypical agents, clozapine, improves at least some negative symptoms (Carpenter et al. 1995; Meltzer 1995) and some neurocognitive deficits (Mortimer and Dye 1997; Potkin et al. 1997; Stone et al. 1997) in severely ill, treatment-refractory patients. Although the toxicity of clozapine precedes its use in the absence of clear psychotic symptoms, the post-clozapine agents—risperidone, olanzapine, and quetiapine—may all improve negative symptoms in patients (Marder and Meibach 1994; Beasley et al. 1996; Small et al. 1997), and risperidone appears to improve some neurocognitive deficits (Green et al. 1997; Lindenmayer et al. 1997).

Clearly, knowledge about the effects of these novel agents in patients is nascent, but the intriguing hints about their effects on negative symptoms and neurocognitive deficits, coupled with their acceptable safety profile, suggests that they might be reasonable candidates for a therapeutic trial in schizotaxic relatives. Moreover, other experimental agents may also be appropriate after more is learned about their properties.

Currently, however, there are several obstacles to the treatment of schizotaxia with atypical antipsychotic medications. In prior studies of schizophrenia patients, improvements in neuropsychological functioning were modest. Moreover, the response of negative symptoms relative to that observed for conventional neuroleptics could have been due to the milder side effects of the atyp-
ichological drugs, which lead to fewer secondary negative symptoms. Thus, because of the limitations of extant work, strong conclusions about the value of atypical antipsychotics for the treatment of schizotypic traits must await future studies using more sensitive measures.

If pharmacological treatment studies of schizotypia proceed, careful pilot investigations would need to assess the potential occurrence of side effects and clarify the dose and titration schedules suitable for schizotypic people. A very cautious approach to this potential use of antipsychotics is especially warranted given reports of spontaneous dyskinesias in schizotypal subjects (Cassady et al. 1998), and widespread neurological abnormalities in nonpsychotic relatives of patients with schizophrenia (Kinney et al. 1986; Kinney et al. 1991; Ismail et al. 1998). Assuredly, proposed studies of antipsychotic treatment would need to weigh the potential benefits of reducing schizotypic symptoms against the risks for drug-induced side effects.

Developing treatments for schizotypia could have several implications. Effective therapies, be they psychological or psychopharmacological, might improve the neuropsychological deficits and negative symptoms typically found in relatives. If Cornblatt and Keilp's (1994) model is correct, improvements in these domains should lessen the distress of the individuals themselves and allow them to function better in family, occupational, and societal roles. Moreover, improving the welfare of schizotypic family members would indirectly benefit their relatives with schizophrenia by decreasing stress in the home and facilitating the progress of family interventions.

Our discussion of the treatment of schizotypia raises an additional question: Do schizotypic persons seek treatment for themselves other than around dealing with a relative with overt schizophrenia? Because of the dearth of data on this issue, a definitive answer awaits future research. Such research should consider several possibilities. Many relatives of schizophrenia patients will deny pathology in themselves, either to avoid identifying with their schizophrenia relative or because they do not experience disability or distress from schizotypic phenomena. When viewed in contrast to the intense adverse outcomes of schizophrenia, the experience of schizotypia may not feel much different from normal. We will not know if these people want or need treatment until appropriate research is completed.

We must also consider that many schizotypic people do not have a relative with schizophrenia. This occurs because of the play of chance: If a family transmits schizophrenia genes, members are at increased risk for schizophrenia, but not all such families will have a member with schizophrenia. Although, such schizotypic people should theoretically exist, they have never been studied. Thus, we await future research to answer a variety of intriguing questions: Do schizotypic people show up in mental health clinics? If so, are they diagnosed with schizotypal personality disorder? Or do their attentional difficulties lead to a diagnosis of attention deficit hyperactivity disorder? Do life failures associated with schizotypic deficits lead to depression?

The treatment of schizotypic adolescents: Can schizophrenia be prevented? It is intriguing to wonder whether our clinical reformulation of schizotypia has implications for the primary prevention of schizophrenia, although speculative. To move from speculation to a preventive trial, we would need to establish at least two facts: (1) that it is possible to accurately define the population at risk for schizophrenia, and (2) that there is a compelling rationale for the proposed preventive treatment.

Can the onset of schizophrenia be predicted? Because a primary prevention trial would target persons at high risk for schizophrenia, its success presupposes a method of defining that risk. A simple method would be to choose adolescent children or siblings of schizophrenia patients. This group has a ten-fold elevated risk for the disorder and is entering the age period of greatest risk for the onset of psychosis. But even though the elevation in risk for this group is substantial, only 10 percent would be expected to develop schizophrenia or a related psychotic disorder. This magnitude of risk is not sufficient for defining the at risk population for preventive trials (unless there was a low-risk treatment that was inexpensive to administer).

Fortunately, research suggests that measures of schizotypia may improve risk prediction to the level where it would be useful in defining populations at very high risk for schizophrenia. For example, in two independent studies of children of schizophrenia patients, Fish (1992), described a syndrome of motor abnormalities that predicted subsequent schizophrenia or related disorders. Similarly, in both the Copenhagen and New York high risk projects, neuromotor impairment predicted the onset of schizophrenia (Olin and Mednick 1996; Erlenmeyer-Kimling 1997). These findings are consistent with Walker and Lewine's (1990) finding of poorer fine and gross motor coordination in videotapes of children who subsequently developed schizophrenia. In addition to neuromotor impairment, attentional deficits also have been found to predict subsequent schizophrenia and related disorders (e.g., L. Erlenmeyer-Kimling, personal communication, 1997).

Given the established link between neuropsychological and social impairment in child relatives, it is not surprising that psychosocial dysfunction also predicts subsequent schizophrenia and related disorders. In the Israeli high risk study, subjects who eventually developed schizophrenia-related disorders had been shy and withdrawn or
aggressive and antisocial as children (Hans et al. 1992). Walker and Lewine's (1990) videotape study described the children who developed schizophrenia as having had poorer eye contact, more negative affect, and diminished social responsiveness. Similarly, in the Copenhagen high risk study, teacher-rated social behaviors were predictive of subsequent schizophrenia (Olin and Mednick 1996).

Thus, among children of schizophrenia patients, schizotypal traits may predict subsequent psychosis. Yet, more needs to be known about the diagnostic accuracy of schizotypal traits—that is, their sensitivity and specificity as predictors of psychosis (Faraone and Tsuang 1994)—before they can be used in prevention trials. Many of the studies reviewed above are difficult to interpret because the outcome they predict is rather broad (i.e., schizophrenia and related disorders). Because trials with antipsychotics would not be warranted for preventing some related disorders (e.g., schizotypal personality), future work needs to precisely estimate the degree to which schizotypy can predict schizophrenia. Moreover, because no diagnostic criteria are available for schizotypy, it is not possible to compare the diagnostic accuracy of schizotypy and schizotypal personality as predictors of psychosis. Future work will need to address this issue.

Theoretically, risk prediction should dramatically improve after molecular genetic studies discover genes for schizophrenia. Notably, linkage studies have discovered regions of the genome that may harbor schizophrenia genes. Four promising chromosomal regions are: 22q11-q13, 6p23, 8p22-21, 15q13-q14, and 10p14-p12 (Pulver et al. 1994; Straub et al. 1995, 1998; Wang et al. 1995; Schizophrenia Collaborative Linkage Group (Chromosome 22) 1996; Schizophrenia Linkage Collaborative Group for Chromosomes 3 and 8 1996; Freedman et al. 1997; Faraone et al. 1998; Leonard et al. 1998; Schwab et al. 1998). Although these findings are promising, no schizophrenia gene has yet been found. After geneticists identify the mutations leading to schizophrenia, these results can be used in combination with schizotypal signs to delineate a group at very high risk for the disorder.

Is there a compelling rationale for a preventive intervention? Although a reasonably accurate ability to predict who will develop schizophrenia is a necessary precondition for prevention trials, it is far from sufficient. There also needs to be a compelling rationale to support an attempt at preventive treatment. In this section we examine possible rationales for psychosocial and psychopharmacologic interventions but emphasize that more research is needed to clarify the potential efficacy of either approach.

Theoretically, psychosocial interventions could choose two foci for intervention: the at-risk individual and the individual's environment. On one hand, such interventions might help the at-risk person withstand the stressful situations that are inherent in life but may be toxic to people predisposed to schizophrenia. On the other hand, since some data, albeit controversial, suggest that the nature of family relationships may be a risk factor for symptoms of schizophrenia (e.g., Goldstein 1987), family interventions might reduce stressors that affect vulnerable family members.

But studies of family interaction must be interpreted cautiously. Rather than being causes of subsequent schizophrenia, family relationships may be influenced by the negative symptoms, neurocognitive dysfunction or psychosocial impairments of the at-risk schizotypic individual or by the effects that these features produce among other family members who may never themselves develop schizophrenia. If a higher genetic risk for schizophrenia leads to a greater expression of schizotypal traits, then measures of stress in the family might well be correlated with the level of genetic vulnerability in the family. If so, then any apparent causal link between the nature of family relationships and subsequent schizophrenia in family members might be spurious.

Clearly, further research is needed to create a scientific foundation for potentially preventive psychosocial interventions. In addition, the possibility that psychopharmacologic approaches might improve the stress tolerance of at-risk persons should also be considered. As researchers begin to address this lacuna in the literature, they will likely develop several research strategies. One idea would be to consider the possibility that treatment studies of schizotypal adults might inform prevention trials for schizotypic adolescents.

This research strategy assumes that (1) adult schizotypia provides a suitable model of the pathophysiology of premorbid schizophrenia, and (2) treatments that ameliorate adult schizotypia do so through neural mechanisms involved in the onset of psychosis in schizotypic adolescents. If neurobiological studies can verify this hypothesis, then an effective medication for adult schizotypia might be the logical choice for a primary prevention trial of schizophrenia.

That psychopharmacologic treatment might prevent the onset of schizophrenia is a logical extension of Wyatt's (1995) idea that early intervention for schizophrenia might alter the course of the illness. His review of 21 controlled studies found that patients who had been treated with antipsychotic medication during their first or second hospitalization had a better outcome than patients who had not been treated early in the course of the 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 treatment mitigates the social consequences of schizophrenia psychopathology, which may result in better outcome by allowing for the easier re-integration of patients into their social networks. This line of reasoning has motivated the creation of early detection and intervention projects seeking to treat schizophrenia patients during their prodrome or first episode (Green and Schildkraut 1995; Falloon et al. 1996; McGlashan 1996; McGlashan and Johannessen 1996; McGorry et al. 1996; Olin and Mednick 1996; Vaglum 1996; Yung et al. 1996).

More work is needed to determine if early treatment with novel antipsychotics exerts a neuroprotective effect or if its success is mediated through social factors. If neuroprotective effects can be shown for first episode schizophrenia patients, is it possible that pharmacological treatment would have neuroprotective effects for schizotaxic adolescents. If so, would the medications protect them from the first onset of psychosis? Although this possibility is intriguing, it is hypothetical and faces several obstacles. Although the benefits of preventing psychosis are clear, a case must be made that they outweigh the risks of treating schizotaxic adolescents with antipsychotic medication. These medications have some side effects in adults, and their effects on adolescent development are unknown. For these reasons, any proposed preventive intervention for schizotaxic adolescents would demand a high level of ethical scrutiny and would presuppose a compelling rationale for any proposed treatment along with the ability to accurately predict who will and who will not develop schizophrenia.

Conclusion

Our inquiry into schizotaxia yields clear conclusions from prior work and intriguing hypotheses for future study. Schizotaxia, we conclude, is not merely a theoretical construct describing the unknown neural substrate of schizophrenia. Almost 4 decades after Meehl first coined the term, an accumulation of research reveals schizotaxia to be a clinically consequential condition. Indeed, the negative symptoms, neuropsychological deficits and psychosocial disabilities of the schizotaxic person constitute a chronic syndrome that may compromise quality of life and goal attainment.

Because some schizotaxic people meet criteria for schizotypal personality disorder, one might argue for incorporating the former into the latter. But that would blur the meaning of schizotypal personality, which is already a heterogeneous diagnosis. Moreover, cleaving schizotypal personality into groups with and without a family history of schizophrenia creates subgroups that differ on etiologic, neurobiological, and clinical features.

Thus, we propose to join schizophrenia-related schizotypal personality disorder with other cases of schizotaxia. This leaves future research the goal of refining diagnostic criteria to accent the distinction between schizotaxia and schizotypal personality disorder. In particular, although negative symptoms and neuropsychological impairments appear to be hallmarks of schizotaxia, some positive symptoms such as mild thought disorder might also be considered as diagnostic criteria. The validity of proposed diagnostic criteria could be examined in family studies of schizophrenia, but family studies of schizotaxia would also be needed to fully clarify the familial relationship between the two conditions.

Our reformulation of schizotaxia has several clinical implications. In family interventions for schizophrenia, knowledge of schizotypal deficits should help clinicians refine their clinical approach to relatives of schizophrenia patients. Likewise, the psychotherapy of schizotaxia would benefit from the clinical insights of those who work with other neuropsychological disorders. There are, of course, no protocols for the psychosocial therapy of schizotaxia. Their invention is another goal for future research.

Our conclusions are limited in several ways. Because there are no agreed upon diagnostic criteria for schizotaxia, studies that have examined this construct among relatives of schizophrenia patients have not used comparable samples. Many of these studies have examined putative indicators of schizotaxia in samples that include subjects with personality disorders, thus obscuring the relative contributions of schizotaxia and known clinical conditions to the expression of schizotypal traits. Moreover, we have also drawn inferences from studies of schizotypal personality disorder which, as we have discussed in this paper, is itself heterogeneous.

Assuredly, our comments regarding the pharmacotherapy of schizotypic adults and the prevention of schizophrenia are speculative. We view these as clinical hypotheses rooted in a nascent scientific literature. They call for studies of schizotaxia: to describe its genetic roots, to delineate its risk factors, to detail its pathophysiology, and to determine why its outcome is not solely schizophrenia.

References


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