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Neurocognitive and clinical dysfunction in adult Chinese, nonpsychotic relatives of patients with schizophrenia: Findings from the Changsha study and evidence for schizotaxia

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ABSTRACT

Many first-degree relatives of patients with schizophrenia demonstrate deficits in neurocognitive, social, clinical and other dimensions, in the absence of psychosis. Based on a reformulation of Meehl's concept of "schizotaxia" as a clinically meaningful syndrome reflecting liability to schizophrenia, we proposed research criteria in relatives focused on negative symptoms and neurocognitive deficits. Here we assess validity of the syndrome in a sample of Chinese adult relatives by assessing measures of concurrent validity, and by using cluster analysis to test the hypothesis that relatives could be grouped into distinct schizotaxic and non-schizotaxic subgroups based on our diagnostic criteria. Thirty community comparison subjects (CCS) and 189 relatives were evaluated with measures of clinical, cognitive, medical and social function at the Mental Health Institute, Second Xiangya Hospital of Central South University, Changsha (Hunan, China), as part of a larger study to identify and ameliorate symptoms of schizotaxia. Using modified research criteria based on negative symptoms and neurocognitive deficits, 103 relatives did not meet criteria for schizotaxia, and 86 did. The cluster analysis confirmed a two-group solution that corresponded to our non-schizotaxic and schizotaxic groups, but it increased the non-schizotaxic group to 135, and reduced the schizotaxic group to 53. Both schizotaxic groups, but especially the cluster-derived group, showed significant impairment in a variety of independent (i.e. non-criterion related) measures of clinical and social function. These findings provide additional validity for a liability syndrome, and for its utility as an intervention target for strategies aimed at ameliorating both its core and its associated symptoms.

Non-psychotic relatives of individuals with schizophrenia often share milder forms of multidimensional deficits or abnormalities with their ill relatives (Snitz et al., 2006; Braff et al., 2007), consistent with a substantial genetic contribution to the disorder (Tsuang et al., 2008). These abnormalities include neurocognitive (e.g. deficits in declarative memory performance), social (e.g. impaired/abnormal emotion perception and attributional style), clinical (e.g. elevated rates of psychiatric disorders/symptoms among offspring of a parent with schizophrenia), psychophysiological (e.g. impaired 'sensory gating', including prepulse inhibition and P50 paradigms), structural and functional neurobiological (e.g. smaller hippocampi, 'default' network activation), and other dimensions of function that go beyond those used to define DSM-IV schizophrenia or related disorders, supporting the view that schizophrenia is more complex than the diagnostic criteria used to define it reliably (Gottesman and Shields, 1982; Tsuang et al., 2000; Seidman et al., 2003; Gur et al., 2007; Turetsky et al., 2007; Keshavan et al., 2008; Penn et al., 2008; Susan Whitfield-Gabrieli et al., 2009; Stone and Hsi, 2011). The increasing attention directed to the search for these alternate phenotypes, or 'endophenotypes' (e.g., heritable social, psychophysiological or neurocognitive abnormalities), also reflects a growing awareness that multidimensional expressions of psychiatric disorders can advance the search for underlying etiological and modulatory factors, as well as influence approaches to early intervention strategies (Gottesman and Gould, 2003). The identification and validation of one or more liability syndrome to identify

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individuals at greatest risk to develop schizophrenia will be an important, if not critical, step in the development of such interventions. Studies of un-medicated relatives at risk for illness that reveal malleable (e.g., cognitive impairments) abnormalities, offer potentially promising treatment targets.

The search for endophenotypes encompasses at least two interrelated areas of focus. One involves their identification. The most common, initial basis for considering putative endophenotypes centers on identifying differences between non-psychotic relatives of individuals with schizophrenia, and relevant control subjects (Faraone et al., 1995a,b). Considerable effort remains, however, to determine which ones will be useful in distinguishing individuals who are more likely to express psychosis from those who are not. In this regard, other properties of the proposed measures (e.g. effect sizes, and/or statistical sensitivity and specificity) are as important as the demonstration of significant group differences (Faraone et al., 1995a, 2001).

A second issue involves the relative utility of individual variables compared to multivatiate clustering of variables. A recent analysis of clinical high risk (i.e., "putatively prodromal") subjects, for example, showed that relatively specific measures of olfactory identification and spatial memory were more predictive of conversion to psychosis than overall cognitive ability, as assessed by a battery of subtests, or by even more "cognitively dense" individual measures involving verbal memory (Brewer et al., 2006). Several reports also show, however, that composite measures of cognitive function or single measures obtained repeatedly, discriminated patients with schizophrenia from controls more effectively than single measures at a single time point (Gottesman et al., 1987; Faraone et al., 1995a; Kremen and Hoff, 2004). Moreover, Erlenmeyer-Kimling and colleagues showed that a combination of verbal memory, gross motor skills and attention in childhood predicted the subsequent development of schizophrenia in the New York High Risk Study more effectively than any of the measures individually, in part because the combination produced lower false positive rates than did individual measures (Erlenmeyer-Kimling et al., 2000).

The utility of different individual or composite neurocognitive measures in predicting the development of schizophrenia emphasizes two points related to defining a liability syndrome. First, while the initial inclusion of specific measures in the syndrome is likely to be informed empirically by previous studies, the inclusion of the categories or dimensions that encompass those measures (e.g. cognition, social function) is also conceptual in nature. Second, subsequent empirical studies may confirm or disconfirm the validity of the proposed syndrome, and contribute to its modification. Paul Meehl underscored the concept of liability to schizophrenia when he introduced the term "schizotaxia" in 1962 to describe a genetically induced condition that predisposed affected individuals to develop either 'schizotypy' or schizophrenia (Meehl, 1962, 1989). He primarily viewed the vulnerability in neural rather than clinical terms, however. Based on subsequent demonstrations of various abnormalities in non-psychotic relatives, and informed by reliable relationships between variables (as described above), Tsuang and colleagues reformulated schizotaxia as a clinically meaningful and observable syndrome in a subgroup of first-degree biological relatives (Tsuang et al., 1999, 2000, 2010). Subjects who met provisional criteria for schizotaxia had no history of psychosis, did not show evidence of functional decline and did not meet diagnostic criteria for schizotypal personality disorder (Stone et al., 2001), though we proposed similarities to negative schizotypal personality disorder symptoms (Tsuang et al., 2002a,b). Schizotaxia thus differed from a genetic high risk group *per se* in that only a subgroup of relatives met criteria for it, and it differed from schizophrenia, from prodromal (clinical high risk) states, and from schizotypal personality disorder.

It should be noted that although Meehl's seminal characterization of schizotaxia and the nature of liability to schizophrenia contributed significantly to Tsuang's reformulation of the concept (Faraone et al., 2001; Stone et al., 2005), the reformulation was intended to identify related endophenotypes that could be utilized in genetic studies and, eventually, as early intervention targets. It was not intended to assess the utility of Meehl's original conceptualization *per se*, or to assess each component of his model. Consequently, initial research criteria focused on negative symptoms and neurocognitive deficits, which were two functional dimensions that had received considerable study by that time in nonpsychotic relatives of patients with schizophrenia (Tsuang et al., 1999; Faraone et al., 2001), and which were consistent with a growing consensus on the broad, multidimensional nature of endophenotypes or intermediate phenotypes proposed by Gottesman and others (Braff et al., 2007). Many other dimensions of function that are also abnormal in schizophrenia (e.g. deficits in brain structure or function, neurophysiology, metabolism, social function or in other clinical/cognitive functions) were not included in the proposed syndrome initially, but would be considered later if the initial, simpler version of the syndrome receives adequate empirical validation.

We hypothesized that since relatives with schizotaxia share clinical symptoms with their ill relatives (i.e. at least negative symptoms and neurocognitive problems), they might also respond to similar interventions. As a pilot test of this principle, we administered low doses of risperidone for 6 weeks in an open-label, pilot protocol to non-psychotic adults who met criteria for schizotaxia (Tsuang et al., 1999, 2002a,b). The results were encouraging, with improvement in negative symptoms and vigilance in 5 out of 6 cases. A subsequent investigation provided additional validity for the syndrome by demonstrating that schizotaxic relatives had lower function on several independent, clinical measures than relatives who did not meet criteria (Stone et al., 2001). Subsequently, Rybakowski et al. (2007) used similar diagnostic criteria to identify schizotaxia in 7 adult (aged 17–44), never-psychotic, first- or second-degree biological relatives of patients with schizophrenia. Unlike our subjects, these subjects reported a decline in function over the previous year, and neuropsychological problems. Yet, none of them met DSM-IV diagnostic criteria for a schizophrenia-related spectrum disorder. Subjects agreed to take low doses of risperidone for periods of 3–7 years. Similar to our results, all subjects demonstrated improvements in negative symptoms and neuropsychological functions, and also showed improvement in social and vocational function. These findings suggest that the symptoms of a validated liability syndrome might ultimately serve as useful treatment targets for interventions that might alter the development of psychosis, although the nature of treatment (pharmacological or non-pharmacological) will require considerable study.

The current study was designed to replicate or modify the identification of a liability syndrome for schizophrenia in adult, non-psychotic, first-degree biological relatives. Although the pilot study was conducted in Boston, the current study was conducted at the Mental Health Institute, Second Xiangya Hospital of Central South University, Changsha, Hunan Province, People's Republic of China, and will be referred to as the 'Changsha Study'. The change in location reflects both the challenges involved in recruiting subjects locally who meet our provisional criteria, coupled with the opportunity to recruit appropriate subjects through collaborators who were working with larger numbers of schizophrenia families. This report focuses on Phase I of the study, which involved the assessment of neurocognitive and negative symptoms in relatives, and in a group of community comparison subjects (CCS). Additional, non-criterion measures of neurocognition, clinical function and social function were also assessed. Subjects who met