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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

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Contributors

All authors contributed to the project. William Stone designed and directed the study and wrote the first draft of the manuscript. Xiaolu Hsi helped to design the study, translate clinical materials between English and Chinese, norm some of the cognitive measures, direct neurocognitive data collection and write the manuscript. Liwen Tan directed data collection in Changsha, contributed to the design of the study and contributed to the manuscript. Shaochun Zhu coordinated the implementation of the study, helped set up the database, and contributed to the manuscript. Lingjiang Li oversaw data collection in Changsha, helped to design the study and recruit subjects, and contributed to the manuscript. Anthony J. Giuliano worked on the database, designed and implemented the data analytic strategy, performed statistical tests and contributed to the manuscript. Larry J. Seidman contributed to the research design, the conceptual basis of the study, the data analytic study and to the manuscript. Ming T. Tsuang initiated and set up the study, helped direct the implementation of the study, and contributed to the manuscript.

Conflicts of Interest / Disclosures

None to report

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, MacDonald III et al. 2006; Braff, Freedman et al. 2007), consistent with a substantial genetic contribution to the disorder (Tsuang, Stone 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, Stone et al. 2000; Seidman, Pantelis et al. 2003; Stone, Faraone et al. 2005; Gur, Calkins et al. 2007; Turetsky, Calkins et al. 2007; Keshavan, Montrose et al. 2008; Penn, Sanna et al. 2008; Susan Whitfield-Gabrieli, Thermenos et al. 2009; Stone and Hsi in press). 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 syndromes to identify 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, Kremen et al. 1995; Faraone, Seidman et al. 1995). 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, Kremen et al. 1995; Faraone, Green et al. 2001).

A second issue involves the relative utility of individual variables compared to multivariate 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, Wood 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, McGuffin et al. 1987; Faraone, Kremen et al. 1995; 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, Rock 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; Meehl 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, Stone et al. 1999; Tsuang, Stone et al. 2000; Stone, Faraone et al. 2005; Tsuang, Stone et al. 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, Faraone et al. 2001), though we proposed similarities to negative schizotypal personality disorder symptoms (Tsuang, Stone et al. 2002). 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, Green et al. 2001; Stone, Faraone 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, Stone et al. 1999; Faraone, Green 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, Freedman 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, Stone et al. 1999; Tsuang, Stone et al. 2002). 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, Faraone 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 criteria for schizotaxia and agreed to enter Phase II of the study were enrolled in a six-week, double-blind protocol in which they received a low dose of risperidone or a placebo. Results of the drug trial, and of medical assessments, will be reported separately.

The analytic approach in this study consists of two stages. In the first stage, we classify relatives as schizotaxic or non-schizotaxic, using measures and diagnostic criteria that were modified from our previous study for the current sample (described below in the Neurocognitive Criteria subsection of the Methods section). Measurement of concurrent validity is done by comparing group differences on non-criterion measures in similar and different domains. In the second phase, we use cluster analysis to explore possible heterogeneity in the schizotaxic group. We will also use cluster analysis to determine whether a two-group solution corresponding to our non-schizotaxic and schizotaxic classification emerges. Group differences will then be assessed between clusters on the same non-criterion measures used in the first stage, to compare similarities and differences in outcome, and in magnitude of difference (i.e. effect size). This strategy is similar in principle to one utilized by Kremen et al in which they first classified the magnitude and pattern of neuropsychological deficits of subjects with schizophrenia, according to eight neuropsychological functions that were determined conceptually (Kremen, Seidman et al. 2004). They then used cluster analyses to classify individuals into groups that might help understand the heterogeneity of their neuropsychological functioning. The goals of the present study are to: 1) replicate our earlier findings by showing that a significant portion of a larger sample of adult, non-psychotic relatives meet criteria for schizotaxia based on weaknesses in negative symptoms and / or neurocognitive functions; 2) evaluate this conception of schizotaxia for evidence of concurrent validity and group cohesion; and 3) refine the conception empirically through an analysis of group heterogeneity.

Methods

Overview

Because relatives were recruited for assessment of schizotaxia (phase I) and subsequent treatment (Phase II), inclusion/exclusion criteria for Phase I included several items related to possible risperidone treatment in Phase II (reported separately).

Subjects

Relatives

Adult Chinese, non-psychotic, first-degree biological relatives of patients with DSM-IV schizophrenia were recruited mainly through the Mental Health Institute, Second Xiangya Hospital, Central South University, in Changsha. Some subjects were also recruited through local psychiatrists working at other hospitals in Hunan Province. All subjects provided informed consent through the Second Xiangya Hospital as a condition of their participation, and all subjects received financial compensation for their time.

Community comparison subjects (CCS)

Thirty CCS were recruited through local advertisements. Inclusion/exclusion requirements were the same as for relatives, except they could not have a first- or second-degree biological relative with schizophrenia or a related disorder in the schizophrenia spectrum. Subjects in this group were used to provide a benchmark comparison group for schizotaxia but they were not recruited into the drug treatment study in Phase II. Exclusion criteria (described below) that were related to potential interactions with risperidone treatment, therefore, were not applied to this group. These included exclusions related to pregnancy or nursing in women, and to the use of medications that could potentially interact with risperidone.

Inclusion/Exclusion Criteria

Inclusion Criteria—Potential subjects had to: 1) have at least one first-degree biological relative with DSM-IV schizophrenia; 2) be 19–50 years of age; and 3) provide informed consent.

Exclusion Criteria—Potential subjects could not have: 1) an estimated IQ below 80; 2) a lifetime history of a psychotic disorder (assessed with the modules from the Diagnostic Interview for Genetic Studies); 3) a substance abuse diagnosis within 6 months of entry into the study; 4) a head injury with documented loss of consciousness exceeding 5 minutes (or subsequent cognitive deficits); 5) a history of neurologic disease or damage; 6) a medical condition with significant cognitive sequelae; 7) a history of electroconvulsive treatment. Subjects could not: 8) be pregnant or nursing; 9) be unwilling to use adequate contraception for the duration of the study (women only); 10) use alpha-blocker medications; 11) use fluoxetine, paroxetine or any other drugs known to interact with risperidone; or 12) participate in another study with an investigational drug or device, or participate in another study within 30 days prior to enrollment in the current study.

Clinical Criteria

Clinical criteria for schizotaxia included negative symptoms and/or neurocognitive dysfunction, as in earlier studies (Tsuang, Stone et al. 1999). Negative symptoms were assessed through clinical interviews, using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983). To meet the negative symptom criterion, subjects had

to have at least 6 of 25 items rated as at least moderately impaired (i.e. defined as ratings of 3 or higher).

Neurocognitive Criteria

Neurocognitive measures assessed the same or similar cognitive domains as those used in our earlier pilot study. They were modified from those used in our pilot study, however, to include criterion measures for which Chinese versions of the tests were available, and for most measures, versions of tests for which normative values were available for Chinese subjects. The neuropsychological measures included tests of: 1) vigilance/working memory, using a Chinese version of the Stroop Test (Color-Word condition) and Digit Span from the Wechsler Adult Intelligence Scale – Revised, Chinese version; 2) verbal memory, using Delayed Recall from one story from a Chinese version of the Logical Memory subtest from the Wechsler Memory Scale–Revised (WMS-R), and the Savings score from the same test (i.e. percentage of information in Delayed Recall compared to the amount recalled in Immediate Recall); and 3) executive functions, using the computerized version of the 128-card version of the Wisconsin Card Sorting Test (WCST). The WCST was used although appropriate norms in Chinese samples were not available to the best of our knowledge. It was used, however, because its visual, nonverbal stimuli was thought to minimize performance differences in subjects speaking different languages (instructions were in Chinese), adequate norms were available for American samples, and it has been included in other Asian studies of schizophrenia (Goto, Yohimura et al. 2009). Criterion measures included Total Errors and Total Perseverative Errors.

Levels of cognitive deficits required to meet criteria were set initially at the same levels as those required in our pilot study. Those levels were relatively stringent, to reduce false positive cases, and to attain a percentage of cases that we observed previously (about 20–50%) (Faraone, Green et al. 2001). Those criteria required that deficits in at least one of the three cognitive domains equaled or exceeded 2 standard deviations below the expected, age-appropriate mean value. Required deficits in a second cognitive domain equaled or exceeded 1 standard deviation below the expected mean. The utilization of these criteria with the modified battery of tests, however, resulted in the classification of far fewer relatives (i.e. less than a third of the rate obtained in the earlier study). For this reason, the threshold values for each cognitive criterion were reduced to 1 standard deviation below average, in at least one of the three cognitive domains. Subjects could also meet criteria for schizotaxia if they met the negative symptom criterion separately. These criteria yielded rates of 86/189 schizotaxic relatives (46%). The broader ranges of cognitive and clinical function encompassed by these criteria were also intended to facilitate empirical explorations of diagnostic thresholds for schizotaxia.

Supplemental Clinical Assessment

In addition to the clinical diagnostic criteria for schizotaxia, all subjects received portions of the Diagnostic Interview for Genetic Studies (Nurnberger, Blehar et al. 1994) that covered psychosis. The Structured Interview for Schizotypy (Kendler, Lieberman et al. 1989) was used to assess for the presence of schizotypal personality disorder, and for the presence of positive and negative symptoms. The subjects also received other clinical interviews and rating scales. These included the Global Assessment of Functioning Scale (GAF) and the Social Adjustment Scale (SAS). The DSM-IV GAF (American Psychiatric Association 1994) provides a unitary measure of the overall level of functioning, while the SAS (Weissman and Bothwell 1976) provides a global score that covers function in several related areas, such as role performance, interpersonal relations, and levels of satisfaction. The SAS was self-rated, while the GAF was rated by the investigators. The investigator ratings were obtained blindly, as each subject's group assignment (schizotaxic or

nonschizotaxic) was made later, after the independent criteria for schizotaxia were evaluated. Both the GAF and the SAS were used as independent measures of clinical and social function that were used to validate differences between relatives who did and did not meet our preliminary criteria for schizotaxia (Stone, Faraone et al. 2001).

Supplemental Cognitive Assessment

In addition to the cognitive diagnostic criteria for schizotaxia, additional cognitive tests were administered. These included Visual Reproduction from the WMS-R, and experimental Auditory and Visual versions of continuous performance tests (A-CPT and V-CPT, respectively). Each of these tests required the rapid detection of targets over time, and the need to inhibit response to particular targets. These non-criterion cognitive measures, like the non-criterion clinical measures described above, were used to assess the validity of group differences or lack of differences between the schizotaxic and non-schizotaxic relative groups.

Medical Assessment

Medical assessments (e.g. liver function tests, cardiac function through EKGs, blood glucose levels and pregnancy tests) were obtained, in part, to rule out medical contraindications to risperidone treatment. They were also administered to determine general health and vital signs. No individuals were excluded because of medical criteria (presented in a separate report).

Data Analyses

Group differences—These analyses focused on group differences between CCS, schizotaxic relatives and non-schizotaxic relatives. Assessment of group differences center on the clinical and neurocognitive criterion measures for schizotaxia, and on several clinical (GAF), social (SAS) and neurocognitive (e.g. A-CPT, V-CPT) non-criterion measures.

Cluster Analyses—The putative diagnostic criteria for schizotaxia include two broad domains, negative symptoms and cognitive functioning, which in turn were used to classify first-degree relatives into schizotaxic and non-schizotaxic subgroups. Using a statistical cluster analysis procedure, we sought to test the hypothesis that relatives could be grouped into two distinct subgroups based on these criteria. Cluster analysis attempts to identify relatively homogeneous groups of relatives on inclusion criteria and assigns each participant into a respective group. After each participant is sorted into their respective groups, between-group differences were assessed by multivariate analysis of covariance (MANCOVA) with appropriate follow-up tests.

Statistics

Group differences—Demographic differences between groups were analyzed using one-way ANOVAs for continuous variables and chi square tests for categorical variables. Group differences between CCS, schizotaxic and non-schizotaxic relatives were analyzed with multivariate analysis of covariance (MANCOVA). In each model, these measures served as dependent variables. Age was included as a planned covariate in the analyses of dependent variables, to assess the effects of variables known to influence performance in the assessed domains. Follow-up ANCOVAs and post-hoc tests (least square differences (LSD) or Tamhane's) were used to assess group differences when overall effects were significant. Effect sizes were calculated using Cohen's *d* (Cohen 1988).

Cluster Analyses A hierarchical cluster analysis was conducted with SPSS Version 16 using squared Euclidean distance on seven measures (negative symptom load, Digit Span, Stroop

Color-Word, Logical Memory Delayed Recall, Logical Memory Savings Score, WCST Total Errors, & WCST Perseverative Errors). Ward's minimum distance was used to create groups by optimizing the ratio of between-group variance to within-group variance (i.e., groups that were maximally different from each other and maximally homogeneous within group) (Kaufman and Rousseau 1990; Hair and Black 2000). The cluster analysis was conducted to identify patterns of negative symptom and cognitive impairment and assess for the presence of groups based on putative schizotaxia criteria. The number of clusters was thus set *a priori* to two to reflect the expected theoretical distinction between schizotaxic and non-schizotaxic relatives. No constraints were imposed on the numbers of participants in each cluster or the profiles of negative symptoms and neurocognitive performance across groups. Thus, the data were allowed to empirically define the subgroups to address the question of whether the symptom profiles exhibited by relatives segregate into theoretically meaningful subsets.

To determine whether negative symptom indices and/or cognitive scores could be combined reliably to predict group membership, and whether they accurately predicted the cluster group (classification), discriminant function (DF) analysis was also performed. DF analysis maximizes group differences by creating a weighted linear combination of the predictor variables (Kleinbaum, Kupper et al. 1988), such that differences between groups are maximized using weights in the DF. The Wilk's lambda coefficient was computed to test the significance of the DF, and the partial Wilk's lambda was used as a measure of the contribution of individual criterion variables to the DF. The partial Wilk's lambda of a given variable ranges between 1 (when all groups are equal) and 0 (when between groups variability largely outweighs within group variability). All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 16 (SPSS 2008).

Study Design and Quality Assurance Procedures

The protocol consisted of 1–2 sessions that included approximately 3 hours of clinical assessment, 2 hours of neurocognitive testing and 2–3 hours of medical assessments.

Before the study began, a joint meeting was held in Changsha to train site investigators in the protocol and associated procedures. Yearly meetings were held in Changsha to review Quality Assurance procedures, troubleshoot problems and to provide 'refresher' training on clinical and neurocognitive measures. These meetings also helped train and certify new testers. Regular and direct communication between investigators at the Changsha and Boston sites facilitated ongoing quality control, including monthly or biweekly conference calls in the last two years of the study. One of the investigators in Boston, who was both a clinical psychologist and a neuropsychologist, and was also a native speaker of Chinese (XH), ensured the accurate translation of study clinical, self-report and neurocognitive measures.

Institutional Oversight

Data collection occurred at the Mental Health Institute, Second Xiangya Hospital, Central South University, with oversight from researchers in Boston (WSS, XH and SZ) and San Diego (MTT). The proposal was submitted to and approved by the Western Institutional Review Board (WIRB) through a yearly review process that assessed the protocol for its scientific merit, and for ethical concerns related to the use of human subjects. Independently, the IRB at the Second Xiangya Hospital reviewed the protocol for the same concerns. Both committees granted permission to proceed.

Results

Group differences using modified diagnostic criteria

Demographic differences—Table 1 shows that relatives without schizotaxia were modestly but significantly younger than relatives with schizotaxia. All relatives considered together did not differ significantly in age from the CCS group. Although relatives with schizotaxia had significantly less education than relatives without schizotaxia, relatives with schizotaxia did not differ from CCSs. The CCS group also had less education than the relatives without schizotaxia. The proportion of males did not differ significantly in any of the three groups. Due to significant differences in age between the relatives with schizotaxia and the other two groups, age was used as a covariate in subsequent analyses. Although level of education did not differ between the schizotaxia and CCS groups, and education is correlated with features of schizophrenia or liability to schizophrenia, education was used as a covariate to avoid the possibility that performance on selection criteria was attributable to correlated levels of education.

Group differences on diagnostic criterion measures

Table 2 shows group differences for negative symptom and neurocognitive criterion measures for schizotaxia. Note that while some measures showed large or moderate effects between the CCS, non-schizotaxic groups and the schizotaxic group (e.g. Logical Memory Delayed Recall; number of SANS items rated 3 or higher; WCST Perseverative Errors), others did not differentiate the groups significantly (e.g. WCST Total Errors). This reflects, in part, the heterogeneous nature of the neurocognitive criteria, in which some subjects met criteria based on deficits in some measures, while others met it based on other measures.

Group differences on non-diagnostic criterion measures

Table 3 demonstrates group differences on non-criterion neurocognitive, clinical and social measures. The groups differed significantly in estimates of overall cognitive ability (IQ scores), but the effect sizes between groups were in the small to moderate range for this measure, and none of the individual group comparisons were significant (all pairwise comparisons were < 0.06). Nevertheless, the schizotaxic group performed more poorly on a wide range of neurocognitive tests than either the CCS group or the non-schizotaxic group, with effect sizes ranging from small to large. Group differences were even more prominent for independent clinical (DSM-IV GAF score) and social (SAS total score) measures, as were evident by large effect sizes.

Group differences using cluster-derived schizotaxia and non-schizotaxia groups

Overview of cluster analysis of schizotaxia criterion scores—Results of the cluster analysis showed that the initial, theoretically-derived, two-cluster solution produced a meaningful classification of the first-degree relatives (Group 1: $n = 135$; Group 2: $n = 53$; one participant was an outlier based on performance on the Logical Memory subtest, and could not be classified reliably into either group). This solution classified 28% of relatives as schizotaxic, close to the value we observed previously in our pilot study (30%) (Stone, Faraone et al. 2001) and our initial study of relatives (Faraone, Seidman et al. 1995). Because a large dominant cluster may sometimes indicate that too few clusters were requested (Hays 1994), the dendrogram was examined to determine whether Group 1 could be split into more clusters. Additional cluster analysis was performed with the number of clusters set to three and four, respectively, allowing for expression of greater heterogeneity in the sample. The resulting solutions produced highly unbalanced groups (e.g., $n_s < 4$), and were not regarded as meaningful. Thus, the original two-cluster solution was regarded as

most meaningful given that it most optimally identified a set of subgroups that minimized within-group variation and maximized between-group variation.

Moreover, a direct discriminant function (DF) analysis was performed using the clinical and six cognitive criterion variables as predictors of membership in the two cluster groups. The DF accounted for 100% of the variance between the two groups, $F(2, 186) = 490.1$, Wilk's lambda = 0.159, $p < .001$. Both the number of negative symptoms greater than 3 and WCST Perseverative Errors T -score were significant in the DF analysis, while the other five cognitive criterion variables did not contribute significantly to the DF analysis.

The means and standard deviations for each of the cluster groups and the CCS on the demographic, clinical and cognitive variables of interest are presented in Tables 4–6. Consistent with the theoretical model and based on the group means observed in the cluster analysis, the first group was labeled “Non-Schizotaxic” and was marked by the relative absence of moderately severe negative symptoms. The second group was labeled “Schizotaxic” and included a smaller group of subjects than that obtained by applying the modified inclusion criteria (53 subjects versus 86). Notably, the putatively schizotaxic group derived from cluster analysis included all 40 subjects who met inclusion criteria based on negative symptom severity ($n = 22$) or both negative symptom and cognitive dysfunction ($n = 18$) criteria. Thirteen of the 46 (28%) cognitive dysfunction only participants were also included in Cluster 2. In effect, 32 subjects were reassigned to the “Non-Schizotaxic” group who were previously included in the “Schizotaxic” group (one subject was omitted as noted above due to an outlying value on a cognitive measure), and reassigned subjects were initially included in the latter group based on modified cognitive criteria alone.

Demographic Analyses—As shown in Table 4, the clusters differed significantly on education only; unlike the original groups, age was not significantly different. As noted above, education was included as a covariate in the analyses. Age was retained as a covariate in the MANCOVA to examine cluster group differences on each of the criterion and non-criterion measures to be consistent with the prior analyses.

Group differences on diagnostic criterion measures

Inspection of Tables 2 and 5 shows a similar pattern of findings on the criterion measures for the initially determined and cluster-derived relative groups. In each instance, some neurocognitive measures and the negative symptoms showed poorer performance in the schizotaxic relatives. Two quantitative differences were also apparent, however. First, effect sizes between the schizotaxic group and CCS or the non-schizotaxic group were either similar or smaller in the cluster-derived groups for most of the neurocognitive measures (Table 5). Second, the effect size of the difference between the schizotaxic group and the other two groups on the SANS was markedly increased in the cluster-derived groups.

Group differences on diagnostic criterion measures

Inspection of Tables 3 and 6 shows a pattern that is similar to that shown by Tables 2 and 5. When the cluster-derived groups are compared for performance on other neurocognitive measures and on independent (i.e. non-criterion-based) clinical and social measures of function, the schizotaxic group performed more poorly than the other groups. The magnitude of the effect sizes on neurocognitive measures was either the same or modestly smaller than it was in the initial composition of the groups (Table 6). The effect sizes of independent measures of clinical or social function were larger.

Discussion

The main findings of this study are two-fold. First, they show that adult, non-psychotic, first-degree biological relatives of individuals with schizophrenia who are classified as schizotaxic also show deficits in other, non-criterion-related clinical and social measures of function. The generalization of these results to broader dimensions of function than those used to define it provides concurrent validity for a syndrome of liability to schizophrenia. The generalization of deficits using a modified set of diagnostic criteria for schizotaxia also replicates in principle a previous study in which we demonstrated generalization using some of the same measures, including the SAS and the GAF (Stone, Faraone et al. 2001). In addition, both the cluster analysis and the DFA provided additional validity for the syndrome of schizotaxia by confirming that the two-cluster solution was both meaningful and corresponded well to the clinical definition of the schizotaxia and non-schizotaxia groups.

More generally, these findings are consistent with a large literature in a subset of relatives showing impairments in neurocognitive, social, clinical and other domains, including domains that are associated with the subsequent development of psychosis (Stone, Faraone et al. 2005; Braff, Freedman et al. 2007). These results have at least four significant implications. First, they indicate that a syndrome of liability for schizophrenia might be identifiable that is distinct conceptually from other genetic high risk and clinical high risk groups. It differs from genetic high risk groups (i.e. the population of all first degree relatives of individuals with schizophrenia) based on the presence of specific clinical symptoms and neurocognitive deficits. It differs from clinical high risk conditions such as the prodrome in that it is conceptualized as a more stable, life-long condition for most individuals, with fewer positive symptoms. A second implication of these findings is that a validated syndrome would make a useful treatment target for strategies aimed at ameliorating its component symptoms. This might be useful for any relative who shows symptoms of schizotaxia, and particularly for those who show neurocognitive deficits that might be amenable to either psychopharmacologic remediation or to other methods of cognitive enhancement (Eack, Greenwald et al. 2009). Related to this point, if schizotaxia or other putative syndromes of liability are eventually validated in adolescents or children, then the possibility of moderating or preventing the development of schizophrenia through interventions aimed at reducing liability symptoms becomes a more feasible strategy. It should be noted that as the field progresses to this point, it will also become critical to progress in outreach and other strategies to facilitate the delivery of such services to the individuals, and to the families of individuals, who will benefit from them.

The similarity of the findings obtained between our pilot work in Boston and our larger study in China reflects a third, cross-cultural implication of these findings. Like schizophrenia itself, which has similar rates of occurrence and clinical symptoms around the world, our findings suggest that symptoms related to the liability for schizophrenia are also similar in subjects with diverse geographic, racial and cultural backgrounds.

Finally, a fourth implication of these findings is an ethical one that may be posed as a question: When is it useful to identify an individual as being at risk for a disorder that he / she might not develop, and when is it harmful? The benefits of reducing functionally impairing symptoms or more importantly, preventing the development of schizophrenia, likely exceed the costs of labeling someone as being at risk. However, uncertainty about the functional outcome means that decisions would also need to be made about when the level of risk justifies the risks of the intervention itself and the classification / diagnosis of being in an at-risk state.

The second main finding of this study is that the utility of the liability syndrome can be refined. The cluster analysis added an empirical component to the composition of the schizotaxic groups, which had been defined previously through an empirically-informed, but conceptual process. The procedure decreased the heterogeneity of the schizotaxic group, which increased its cohesion and distinctiveness from the non-schizotaxic relative group and the non-relative control group (CCS). This was demonstrated by the increased effect sizes in the cluster-derived schizotaxic group, compared to the effect sizes for the clinically defined groups. Among the non-criterion measures of social and clinical function, for example, the effect size (d') doubled (from 1.20 to 2.44) when the initial schizotaxia group was reformulated using the cluster analysis (compared to the CCS group). The change in effect size for negative symptoms (which was a criterion measure) was even more prominent. Although it was large using the initial criterion (1.43), it tripled in the cluster-derived schizotaxic group (4.35). Moreover, increased cohesion of the reformulated groups was reflected by modest reductions in the effect sizes of several neurocognitive measures, which likely reflected the removal of putatively false positive members of the schizotaxic group, and their reassignment to the non-schizotaxic group.

The relative strength of the negative symptom criterion compared to most of the neurocognitive criteria in distinguishing the schizotaxic relatives from non-schizotaxic relatives and from the CCS has implications for its continued evolution. One of these implications involves the relative value of using individual measures of neurocognitive function as criterion measures. The current findings show the approach has merit. For example, using the criterion of 1 standard deviation below the expected mean of any of the neurocognitive criterion measures, schizotaxic relatives showed moderate or large differences in performance from non-schizotaxic and CCS on several independent measures of sustained auditory and verbal vigilance, and visual declarative memory (Table 3). This point notwithstanding, however, the use of multiple, alternative, neurocognitive criterion measures also contributed to heterogeneity in the schizotaxic group using the earlier criteria, because only subgroups of individuals show deficits in particular measures. This means that while a neurocognitive criterion for schizotaxia may be met by an individual, the group effect for that measure may be small, which has the potential to dilute the functional significance and the diagnostic potential of neurocognition in both schizophrenia (Kremen, Seidman et al. 2004) and in a syndrome reflecting the liability to schizophrenia.

In contrast to several of the neurocognitive measures, the negative symptom criterion was more unitary, as reflected by the single SANS measure used to assess it. In accordance with the earlier diagnostic criteria, it was also more severe, as the criterion of demonstrating at least 6 SANS items rated 3 or higher was presumed to reflect a moderate degree of impairment. These features contributed to the large differences obtained between the schizotaxic group and the other groups in functional domains that were affected by elevated levels of negative symptoms. Based on the observed differences between the neurocognitive and negative symptom criteria in this study, several approaches might be utilized to decrease heterogeneity in the neurocognitive diagnostic criteria, and to increase validity of the overall syndrome. One such approach includes clustering methods such as that utilized in this report. Another would be to develop and assess the use of cognitive composite scores as criterion measures. As noted previously, such neurocognitive composite measures are often more useful at discriminating subjects with schizophrenia from controls than are individual cognitive measures, and are often more useful than other symptom-based or other types of measures (Faraone, Kremen et al. 1995; Faraone, Seidman et al. 1995; Kremen and Hoff 2004; Kremen, Seidman et al. 2004). Moreover, this approach (e.g. combining individual test scores to produce cognitive domains) has utility in describing neurocognitive functioning in at-risk populations (Seidman, Giuliano et al. 2006), and in predicting which prodromal subjects are most likely to progress to psychosis (Keefe, Perkins et al. 2006).

The issue of neurocognitive composite scores is related to a more general issue raised by the current findings. Most of the specific neurocognitive tests proposed as criterion measures in our pilot study were not utilized in the current study because they were not normed in China. Instead, available tests that measured similar domains were employed. While test differences probably contributed to initial differences in the obtained rates of schizotaxia, neurocognitive test performance in the schizotaxia group (defined in either the initial or in the cluster-derived manner) was associated with performance on multiple, other, non-criterion tests (see Tables 3 and 6). Consistent with the broad range of cognitive deficits that often characterizes schizophrenia (Seidman, Cassens et al. 1992), this observation demonstrates that the neurocognitive deficit in schizotaxia is also broader and more robust than impairment on specific measures in specific tests, though individual tests may have particular diagnostic significance (Brewer, Wood et al. 2006). The question of whether schizotaxia would gain more sensitivity or predictive power from using individual test scores as criteria, combinations of tests into relatively specific cognitive domain composites (e.g. attention or processing speed), or a more general cognitive composite, is an empirical one. Similarly, the question of whether neurocognitive measures would have greater utility if they were weighted or organized more hierarchically warrants consideration.

Overall, many unanswered questions about schizotaxia remain. In addition to the measurement issues discussed above, the relationship of schizotaxia to other putative dimensions of liability (e.g. abnormal brain structure and function, formal thought disorder and subjective experiences in relatives,) is but one of many examples. Both the construct and the ways in which it is measured will likely continue to evolve, with the likelihood that other liability syndromes will be proposed and validated as well. Nevertheless, the current findings add to the validity and clinical significance of this proposed syndrome in particular, and to the more general proposition that putative liability syndromes for schizophrenia can be defined using specific operational criteria. In so doing, they strengthen the view that treatment targets related to the liability for schizophrenia can be identified and possibly ameliorated.

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
- Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Iowa: The University of Iowa; 1983.
- Braff DL, Freedman R, et al. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin*. 2007; 33:21–32. [PubMed: 17088422]
- Brewer WJ, Wood SJ, et al. Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. *Schizophrenia Bulletin*. 2006; 32:538–555. [PubMed: 16782759]

- Cohen, J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, N.J.: Lawrence Earlbaum; 1988.
- Eack SM, Greenwald DP, et al. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric Services*. 2009; 60:1468–1476. [PubMed: 19880464]
- Erlenmeyer-Kimling L, Rock D, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *American Journal of Psychiatry*. 2000; 157(9):1416–1422. [PubMed: 10964857]
- Faraone SV, Green AI, et al. "Schizotaxia": Clinical Implications and New Directions for Research. *Schizophrenia Bulletin*. 2001; 27:1–18. [PubMed: 11215539]
- Faraone SV, Kremen WS, et al. Diagnostic accuracy and linkage analysis: How useful are schizophrenia spectrum phenotypes? *American Journal of Psychiatry*. 1995; 152:1286–1290. [PubMed: 7653682]
- Faraone SV, Seidman LJ, et al. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A diagnostic efficiency analysis. *Journal of Abnormal Psychology*. 1995; 104:286–304. [PubMed: 7790631]
- Goto N, Yohimura R, et al. Associations between plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) and negative symptoms or cognitive impairments in early-stage schizophrenia. *Human Psychopharmacology*. 2009; 24:639–645. [PubMed: 19946939]
- Gottesman, McGuffin P, et al. Clinical genetics as clues to the "real" genetics of schizophrenia (a decade of modest gains while playing for time). *Schizophrenia Bulletin*. 1987; 13(1):23–47. [PubMed: 3474774]
- Gottesman II, Gould TDD. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Gottesman, II.; Shields, J. *Schizophrenia: The Epigenetic Puzzle*. Cambridge: Cambridge University Press; 1982.
- Gur RE, Calkins ME, et al. The Consortium on the Genetics of Schizophrenia (COGS): Neurocognitive Endophenotypes. *Schizophrenia Bulletin*. 2007; 33:49–68. [PubMed: 17101692]
- Hair, JF.; Black, WC. Cluster analysis. In: Grimm, LG.; Yarnold, PR., editors. *Reading and understanding more multivariate statistics*. Washington, D.C: American Psychological Association; 2000. p. 147-205.
- Hays, WL. *Statistics*. Fort Worth, Texas: Harcourt Brace; 1994.
- Kaufman, L.; Rousseau, P. *Finding Groups in Data*. New York: Wiley; 1990.
- Keefe RSE, Perkins DO, et al. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophrenia Research*. 2006; 88:26–35. [PubMed: 16930949]
- Kendler KS, Lieberman JA, et al. The structured interview for schizotypy (SIS): A preliminary report. *Schizophrenia Bulletin*. 1989; 15(4):559–571. [PubMed: 2623438]
- Keshavan MS, Montrose DM, et al. Psychopathology among offspring of parents with schizophrenia: relationship to premorbid impairments. *Schizophrenia Research*. 2008; 103:114–120. [PubMed: 18442896]
- Kleinbaum, DG.; Kupper, LL., et al. *Applied Regression and Other Multivariate Methods*. Boston: PWS-Kent Publishing; 1988.
- Kremen, WS.; Hoff, AL. Neurocognitive deficits in the biological relatives of individuals with schizophrenia. In: Stone, WS.; Faraone, SV.; Tsuang, MT., editors. *Early Clinical Intervention and Prevention with Schizophrenia*. Totowa, New Jersey: Humana Press; 2004. p. 133-158.
- Kremen WS, Seidman LJ, et al. Heterogeneity of schizophrenia: a study of individual neuropsychological profiles. *Schizophrenia Research*. 2004; 71:307–321. [PubMed: 15474901]
- Meehl PE. Schizotaxia, schizotypy, schizophrenia. *American Psychologist*. 1962; 17:827–838.
- Meehl PE. Schizotaxia revisited. *Archives of General Psychiatry*. 1989; 46:935–944. [PubMed: 2552952]
- Nurnberger JI Jr, Blehar MC, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. *Archives of General Psychiatry*. 1994; 51:849–859. [PubMed: 7944874]

- Penn DL, Sanna LJ, et al. Social Cognition in Schizophrenia: An Overview. *Schizophrenia Bulletin*. 2008; 34:408–411. [PubMed: 18375928]
- Seidman LJ, Cassens GP, et al. Neuropsychology of schizophrenia. In: White, RF., editor. *Clinical Syndromes in Adult Neuropsychology: The Practitioner's Handbook*. Elsevier Science Publishers B.V.; 1992. p. 381-449.
- Seidman LJ, Giuliano AJ, et al. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside adolescent high risk studies. *Schizophrenia Bulletin*. 2006; 35:507–524. [PubMed: 16707777]
- Seidman LJ, Pantelis C, et al. A review and a new report of medial temporal lobe dysfunction as a vulnerability indicator for schizophrenia: A MRI morphometric family study of the parahippocampal gyrus. *Schizophrenia Bulletin*. 2003; 29:803–808. [PubMed: 14989416]
- Snitz BE, MacDonald AW III, et al. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin*. 2006; 32:179–194. [PubMed: 16166612]
- SPSS. SPSS for Windows, Rel. 16. Chicago: SPSS Inc.; 2008.
- Stone WS, Faraone SV, et al. Concurrent validation of schizotaxia: a pilot study. *Biological Psychiatry*. 2001; 50(6):434–440. [PubMed: 11566160]
- Stone WS, Faraone SV, et al. Searching for the liability to schizophrenia: concepts and methods underlying genetic high-risk studies of adolescents. *J Child Adolesc Psychopharmacol*. 2005; 15(3):403–417. [PubMed: 16092907]
- Stone WS, Faraone SV, et al. Searching for the liability to schizophrenia: concepts and methods underlying genetic high-risk studies of adolescents. *Journal of Child and Adolescent Psychopharmacology*. 2005; 15:403–417. [PubMed: 16092907]
- Stone WS, Hsi X. Declarative memory deficits and schizophrenia: Problems and prospects. *Neurobiology of Learning and Memory*. (in press).
- Susan Whitfield-Gabrieli S, Thermenos HW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Science of the United States of America*. 2009; 106:1279–1284.
- Tsuang MT, Stone WS, et al. Prevention of schizophrenia. *Expert Review of Neurotherapeutics*. 2010; 10:1165–1174. [PubMed: 20586696]
- Tsuang MT, Stone WS, et al. Towards reformulating the diagnosis of schizophrenia. *American Journal of Psychiatry*. 2000; 147:1041–1050. [PubMed: 10873908]
- Tsuang, MT.; Stone, WS., et al. Gene-environment interactions in mental disorders: A current view. In: Freeman, H.; Stansfeld, S., editors. *The Impact of the Environment on Psychiatric Disorder*. London: Routledge; 2008. p. 27-51.
- Tsuang MT, Stone WS, et al. Treatment of nonpsychotic relatives of patients with schizophrenia: Four case studies. *Biological Psychiatry*. 1999; 41:1412–1418. [PubMed: 10356622]
- Tsuang MT, Stone WS, et al. An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophrenia Research*. 2002; 54(1–2):169–175. [PubMed: 11853991]
- Tsuang MT, Stone WS, et al. Treatment of nonpsychotic relatives of patients with schizophrenia: six case studies. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*. 2002; 114(8): 943–948. [PubMed: 12457391]
- Turetsky BI, Calkins ME, et al. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophrenia Bulletin*. 2007; 33:69–94. [PubMed: 17135482]
- Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. *Archives of General Psychiatry*. 1976; 33:1111–1115. [PubMed: 962494]

Table 1

Demographic variables using (modified) initial criteria for schizotaxia¹

Variable/Group	CCS (1) N=30	Non- Schizotaxia (2) N=103	Schizotaxia (3) N=86	Overall Group Differences ² F-Statistic, p	Post-Hoc Group Comparisons ³
Age² (n = 219)	32.1 (10.7)	31.4 (11.1)	35.9 (10.7)	$F = 4.21, p = 0.016$	2 < 3; 1 = 2, 3
Gender N (% Male)	14 (46.7%)	44 (42.7%)	48 (58.5%)	$\chi^2 (2) = 3.26, p = 0.196$	NS
Personal Education	11.5 (2.1)	12.6 (2.8)	11.4 (2.9)	$F = 4.9, p = 0.008$	2 > 1, 3

¹Expressed as means ($\pm$ standard deviations) for all measures except gender and handedness, which are expressed as frequencies with percentages in parentheses.

²ANCOVAs for continuous variables; Gender is Chi-Square.

³Least square means.

Table 2

Group performance on criterion variables using (modified) initial criteria for schizotaxia^{1, 2, 3, 4}

	CCS (1) n=30	Non- Schizotaxia (2) n=103	Schizotaxia (3) n=86	ANCOVA	Pairwise Comparisons ⁶	Effect Sizes ⁷		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F-Statistic p</i>		<i>1-2</i>	<i>1-3</i>	<i>2-3</i>
Neurocognitive Variables								
Digit Span ScS ⁴	12.9 (3.1)	13.2 (2.7)	12.1 (2.9)	F=6.43 <i>p</i> <.001	NS	0.10	0.27	0.39
Stroop Color-Word RS ⁵	34.3 (12.1)	39.7 (10.2)	29.6 (10.2)	F=23.94 <i>p</i> <.001	1, 3 < 2	-0.48	0.42	0.99
LM Delayed Recall SS ⁵	14.1 (4.2)	12.9 (4.5)	8.3 (4.7)	F=22.06 <i>p</i> <.001	3 < 1, 2	0.28	1.30	1.00
LM Savings Score (%) ⁵	92.1 (15.2)	91.9 (57.3)	79.3 (24.2)	F=1.44 <i>p</i> =.223	NS	0.00	0.63	0.29
WCST Total Errors T-Score ⁵	40.4 (12.4)	41.9 (17.9)	38.5 (15.5)	F = 1.36, <i>p</i> = .248	NS	-0.10	0.14	0.20
WCST Perseverative Errors T-Score ⁵	45.0 (13.7)	36.9 (19.7)	38.3 (16.8)	F = 2.93, <i>p</i> = .022	NS (all <i>f</i> /u <i>ps</i> > 0.06)	0.48	0.44	-0.08
Negative Symptom Variable								
SANS Ratings ^{3, 4}	0.20 (0.66)	0.73 (1.2)	3.6 (3.3)	F=28.9 <i>p</i> <0.001	3 > 1, 2	-0.55	-1.43	-1.16

¹ Group means and standard deviations are based on variable raw or standard score, as noted.

² Sample sizes are based on an overall *n* = 219.

³ Statistical tests are based on mixed effects regression models with group as a fixed effect, and age and education as covariates.

⁴ Higher scores denote better performance for all neurocognitive variables; higher SANS scores denote more impaired performance

⁵ ScS=Scaled Score; RS=Raw Score; LM=Logical Memory; WCST=Wisconsin Card Sorting Test; SANS=Scale for the Assessment of Negative Symptoms

⁶ Post-hoc *t*-tests are based on least square means.

⁷ Effect size estimates are based on Cohen's *d* using group raw score means and the pooled standard deviation.

Table 3

Group performance on non-criterion variables using (modified) initial definition for schizotaxia¹, 2, 3, 4

	CCS (1) n=30	Non- Schizotaxia (2) n=103	Schizotaxia (3) n=86	ANCOVA	Pairwise Comparisons ⁶	Effect Sizes ⁷		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>		1-2	1-3	2-3
Neurocognitive Variables								
Estimated IQ SS ⁵	105.3 (13.6)	108.3 (13.3)	101.9 (15.2)	F=12.8, <i>p</i> <0.001	NS (overall F is significant, but all pc's are > 0.06)	-0.22	0.24	0.45
A-CPT OE RS ⁵	13.4 (27.6)	9.68 (11.1)	16.1 (19.1)	F=.661, <i>p</i> =0.620	NS	0.18	-0.11	-0.41
A-CPT RT RS (ms) ⁵	786.1 (27.8)	803.6 (31.0)	808.2 (30.2)	F=10.7 <i>p</i> <0.001	3 < 1, 2	-0.59	-0.76	-0.15
V-CPT OE RS ⁵	5.4 (8.6)	6.9 (11.6)	16.9 (22.5)	F=2.86, <i>p</i> <.024	NS	-0.15	-0.68	-0.56
V-CPT RT RS (ms) ⁵	760.2 (27.7)	772.9 (32.3)	794.6 (41.1)	F=25.5, <i>p</i> <.001	3 > 2 > 1	-0.42	-0.98	-0.59
LM Immediate Recall SS ⁵	15.3 (3.7)	14.2 (4.5)	10.2 (5.1)	F=15.2, <i>p</i> <.001	3 < 1, 2	0.27	1.14	0.83
VR Immediate Recall SS ⁵	10.2 (2.6)	10.5 (2.7)	8.8 (2.9)	F=18.6, <i>p</i> <.001	3 < 1, 2	-0.11	0.51	0.61
VR Delayed Recall SS ⁵	10.1 (2.6)	9.8 (3.1)	7.7 (3.3)	F=22.1, <i>p</i> < 0.001	3 < 1, 2	0.10	0.81	0.66
Clinical / Social Function								
SANS Total Score	19.6 (6.1)	22.9 (10.1)	33.9 (13.4)	F=16.9, <i>p</i> < 0.001	3 > 1, 2	-0.41	-1.37	-0.92
GAF	79.3 (7.4)	75.5 (7.6)	69.4 (9.0)	F=12.37, <i>p</i> < 0.001	3 < 2 < 1	0.51	1.20	0.73
SAS Total Score	58.6 (19.0)	64.6 (21.5)	74.6 (17.8)	F=22.9, <i>p</i> < 0.001	3 > 2 > 1	-0.31	-0.87	-0.50

¹ Group means and standard deviations are based on variable raw or standard score, as noted.

² Sample sizes are based on an overall n = 219.

³ Statistical tests are based on mixed effects regression models with group as a fixed effect, and age as a covariate.

⁴ Higher scores denote better performance for IQ, LM, VR and GAF; Lower scores denote better performance on the A-CPT, V-CPT, SANS and SAS.

⁵ SS=Scaled Score; RS=Raw Score; LM=Logical Memory; IQ=Intelligence Quotient; ACPT=Auditory Continuous Performance Test; OE=Omission Errors; RT=Reaction Time; (ms)=milliseconds; V-CPT=Visual Continuous Performance Test; VR=Visual Reproduction; SANS=Scale for the Assessment of Negative Symptoms; GAF=Global Assessment of Functioning Scale; SAS=Social Adjustment Scale

⁶ Post-hoc *t*-tests are based on least square means.

⁷ Effect size estimates are based on Cohen's *d* using group raw score means and the pooled standard deviation.

Table 4
Demographic variables using cluster-derived schizotaxia and non-schizotaxia groups¹

Variable/Group	CCS (1) N=30	Non- Schizotaxia (2) N=135	Schizotaxia (3) N=53	Overall Group Differences ² F-Statistic, p	Post-Hoc Group Comparisons ³
Age ² (n = 219)	32.1 (10.7)	33.8 (11.0)	32.3 (11.1)	$F = 0.527, p = 0.59(\text{ns})$	ns
Gender N (% Male)	14 (46.7%)	61 (45.2%)	31 (58.5%)	$\chi^2 (2) = 2.75, p = 0.253$	ns
Personal Education	11.5 (2.1)	12.4 (2.8)	11.2 (3.2)	$F = 4.2, p = 0.017$	2 > 1,3

¹Expressed as means ($\pm$ standard deviations) for all measures except gender and handedness, which are expressed as frequencies with percentages in parentheses.

²ANCOVAs for continuous variables; Gender is Chi-Square.

³Least square means.

Table 5

Group performance on criterion variables using cluster-derived schizotaxia and non-schizotaxia groups^{1, 2, 3, 4}

	CCS (1) n=30	Non- Schizotaxia (2) n=135	Schizotaxia (3) n=53	ANCOVA	Pairwise Comparisons ⁶	Effect Sizes ⁷		
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>F</i> -Statistic <i>P</i>		<i>I</i> -2	<i>I</i> -3	<i>I</i> -3
Neurocognitive Variables								
Digit Span SS ⁴	12.9 (3.1)	13.1 (2.7)	11.8 (2.9)	<i>F</i> =6.9 <i>p</i> <.001	3 < 2	-0.07	0.37	0.46
Stroop Color- Word RS ⁵	34.3 (12.1)	35.7 (11.7)	33.2 (10.3)	<i>F</i> =15.7, <i>p</i> < .001	NS	-0.18	0.10	0.23
LM Delayed Recall SS ⁵	14.1 (4.2)	11.5 (5.1)	9.1 (4.7)	<i>F</i> =12.7, <i>p</i> <.001	3 < 2 < 1	0.56	1.12	0.49
LM Savings Score (%) ⁵	92.1 (15.2)	83.4 (26.2)	82.9 (24.5)	<i>F</i> =1.27 <i>p</i> =.284	NS	0.41	0.45	0.02
WCST Total Errors T-Score ⁵	40.4 (12.4)	40.1 (16.9)	40.5 (17.1)	<i>F</i> = .616, <i>p</i> = .651	NS	0.02	-0.01	-0.02
WCST Perseverative Errors T-Score ⁵	45.0 (13.7)	35.9 (17.7)	40.9 (17.7)	<i>F</i> = 3.2, <i>p</i> = .013		0.66	0.26	-0.28
Negative Symptom Variable								
SANS Ratings 3 ⁴	0.20 (0.66)	0.40 (0.77)	6.1 (1.8)	<i>F</i> =276.1 <i>p</i> <0.001	3 > 1, 2	-0.28	-4.35	-4.12

¹ Group means and standard deviations are based on variable raw or standard score, as noted.

² Sample sizes are based on an overall n = 219.

³ Statistical tests are based on mixed effects regression models with group as a fixed effect, and age as a covariate.

⁴ Higher scores denote better performance for all neurocognitive variables; higher SANS scores denote more impaired performance

⁵ SS=Scaled Score; RS=Raw Score; LM=Logical Memory; WCST=Wisconsin Card Sorting Test; SANS=Scale for the Assessment of Negative Symptoms

⁶ Post-hoc *t*-tests are based on least square means.

⁷ Effect size estimates are based on Cohen's *d* using group raw score means and the pooled standard deviation.

Table 6

Group performance on non-criterion variables using cluster-derived schizotaxia and non-schizotaxia groups^{1, 2, 3, 4}

	CCS (1) n=30	Non- Schizotaxia (2) n=135	Schizotaxia (3) n=53	ANCOVA	Pairwise Comparisons ⁶	Effect Sizes ⁷		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>	<i>F</i>	<i>I-2</i>	<i>I-3</i>	<i>2-3</i>
Neurocognitive Variables								
Estimated IQ SS ⁵	105.3 (13.6)	106.4 (13.9)	102.3 (15.6)	F=12.5, <i>p</i> <.001	NS	-0.08	0.20	0.28
A-CPT OE RS ⁵	13.4 (27.6)	10.4 (12.4)	25.1 (54.1)	F=2.7, <i>p</i> =0.024	3 > 2	0.14	-0.27	-0.37
A-CPT RT RS (ms) ⁵	786.1 (27.8)	803.9 (29.3)	809.3 (33.5)	F=6.34, <i>p</i> =0.002	3 > 1	-0.62	-0.75	-0.17
V-CPT OE RS ⁵	5.4 (8.6)	8.5 (13.2)	26.4 (55.5)	F=10.4, <i>p</i> <.001	3 > 1, 2	-0.28	-0.75	-0.55
V-CPT RT RS (ms) ⁵	760.2 (27.7)	778.7 (37.3)	793.4 (38.4)	F=6.1, <i>p</i> <.001	3 > 2 > 1	-0.56	-0.99	-0.39
LM Immediate Recall SS ⁵	15.3 (3.7)	13.0 (4.9)	10.9 (4.9)	F=9.03, <i>p</i> <.001	3 < 2 < 1	0.52	1.01	0.42
VR Immediate Recall SS ⁵	10.2 (2.6)	9.8 (3.1)	9.4 (2.4)	F=16.5, <i>p</i> <.001	NS	0.14	0.32	0.14
VR Delayed Recall SS ⁵	10.1 (2.6)	9.1 (3.4)	8.1 (3.1)	F=19.5, <i>p</i> <.001	3 < 1	0.33	0.49	0.23
Clinical / Social Function								
SANS Total Score	19.6 (6.1)	21.9 (8.8)	43.6 (6.9)	F=73.3, <i>p</i> <0.001	3 > 1, 2	-0.30	-3.69	-2.74
GAF	79.3 (7.4)	76.3 (7.2)	63.7 (5.2)	F=38.9, <i>p</i> <0.001	3 < 2 < 1	0.41	2.44	2.01
SAS Total Score	58.6 (19.0)	65.6 (19.7)	77.8 (19.8)	F=15.9, <i>p</i> <0.001	3 > 1, 2	-0.36	-0.97	-0.60

¹ Group means and standard deviations are based on variable raw or standard score, as noted.

² Sample sizes are based on an overall *n* = 219.

³ Statistical tests are based on mixed effects regression models with group as a fixed effect, and age as a covariate.

⁴ Higher scores denote better performance for IQ, LM, VR and GAF; Lower scores denote better performance on the A-CPT, V-CPT, SANS and SAS.

⁵ SS=Scaled Score; RS=Raw Score; LM=Logical Memory; IQ=Intelligence Quotient; ACPT=Auditory Continuous Performance Test; OE=Omission Errors; RT=Reaction Time; (ms)=milliseconds; V-CPT=Visual Continuous Performance Test; VR=Visual Reproduction; SANS=Scale for the Assessment of Negative Symptoms; GAF=Global Assessment of Functioning Scale; SAS=Social Adjustment Scale

⁶ Post-hoc *t*-tests are based on least square means.

⁷ Effect size estimates are based on Cohen's *d* using group raw score means and the pooled standard deviation.