Published in final edited form as:

Asian J Psychiatr. 2012 March 1; 5(1): 73–82. doi:10.1016/j.ajp.2011.12.001.

Are neurocognitive, clinical and social dysfunctions in schizotaxia reversible pharmacologically?: Results from the Changsha study

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Abstract

The Changsha study identifies adult, non-psychotic relatives of patients with schizophrenia who show deficits in neurocognitive, social, clinical and other dimensions, and who meet provisional criteria for a liability syndrome for schizophrenia ('schizotaxia'). In this study, we investigated whether negative symptoms, neurocognitive deficits, or other measures of clinical and social function in subjects who met our research criteria for schizotaxia were amenable to pharmacological remediation with a low dose (2.0 mg) of risperidone, a second generation antipsychotic medication. One hundred eighty nine relatives were assessed at the Mental Health Institute, Second Xiangya Hospital of Central South University, Changsha (Hunan Province, China), between 12/06 – 12/08. Eighty six of these individuals met modified criteria for schizotaxia, and 36 agreed to enter a 6-week, double-blind, placebo-controlled protocol. ANCOVAs using age and gender as covariates showed significant improvement in the risperidone group (n=20) on neurocognitive function (Wisconsin Card Sorting Test Total Errors and Perseverative Errors) and on a self-report measure of social function (Social Adjustment Scale), compared to the placebo-control group (n=16). Effect sizes were small to medium. Notably,

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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

risperidone effect sizes were larger (medium to large) in a subset of subjects (risperidone=15; placebo=10) whose membership in the schizotaxic group was supported empirically by cluster analysis. Negative symptoms did not change significantly in either analysis. The results are generally consistent with previous open-label investigations of risperidone administration in subjects with schizotaxia, and provide evidence that some neurocognitive and clinical problems are amenable to remediation in non-psychotic relatives of people with schizophrenia.

Subgroups of non-psychotic relatives of patients with schizophrenia show deficits or abnormalities in clinical, cognitive, social, biological and other dimensions of functioning that are similar to, though milder than, those shown in schizophrenia (Keshavan et al., 2010; Stone et al., 2005). These similarities in individuals with an elevated genetic risk for schizophrenia (e.g., adolescent or young adult first-degree biological relatives of people with schizophrenia) raise the question of whether they reflect symptoms of an observable liability syndrome. One way to do so would be to meet DSM-IV diagnostic criteria for a condition that is related to schizophrenia but is milder, like schizotypal personality disorder (SPD). Although most individuals with SPD do not develop schizophrenia (Faraone et al., 2001; Tsuang et al., 1999a), characterizing their liability is important, partly to inform interventions that target their clinical manifestations.

More generally, studies of non-psychotic, non-schizotypal adult relatives of schizophrenic patients who carry the risk for the disorder are important for the development of early interventions for schizophrenia and related conditions in at least two ways. First, they can be studied in order to refine subgroups that may develop schizophrenia. As the accuracy of prediction increases, the potential for targeted early intervention increases. Second, the identification of cognitive, clinical, social and other deficits in non-psychotic relatives may identify individuals who could benefit from treatments or other interventions, regardless of whether they subsequently develop schizophrenia, if they were to seek treatment. While adolescent and young adult non-psychotic relatives of individuals with schizophrenia may show elevated rates of psychopathology as a group (Glatt et al., 2006; Keshavan et al., 2008), they often do not meet criteria for DSM-IV disorders in the schizophrenia spectrum (Stone et al., 2001). Consequently, they may not receive interventions for schizophrenia-related conditions.

Based on Paul Meehl's conceptualization of 'schizotaxia' (Meehl, 1962), we reformulated the concept to propose one such liability syndrome based on observable, clinically meaningful symptoms involving negative symptoms and neurocognitive deficits in non-psychotic adult relatives (Faraone et al., 2001; Tsuang et al., 2000; Tsuang et al., 1999b). Initial tests of concurrent validity were encouraging, as relatives classified as schizotaxic showed poorer performance in independent measures of clinical and social function (Stone et al., 2001). A related issue is whether cognitive or negative symptoms of schizotaxia – and more generally, schizophrenia – are amenable to remediation. Recent studies using a variety of approaches, such as cognitive enhancement therapy (Eack et al., 2009; Eack et al., 2010), have been promising. Novel pharmacological approaches have also shown promise in improving cognition in schizophrenia (Stone and Seidman, 2008).

We considered whether low doses of a second generation antipsychotic medication might also reduce symptoms of schizotaxia (Tsuang et al., 1999b). We reasoned that since relatives classified as schizotaxic shared about 50% of their genes with their ill relatives that they may respond positively to pharmacological interventions that attenuated some negative symptoms and/or neurocognitive deficits in addition to their abilities to reduce positive symptoms in their ill relatives. Several second generation antipsychotic medications, including risperidone, produce modest improvements in neurocognitive function in schizophrenia (Keefe et al., 2007a; Keefe et al., 2007b), although methodological problems

such as practice effects may confound these findings (Goldberg et al., 2011; Goldberg and Gomar, 2009). In an initial investigation, we administered low doses of risperidone (up to 2.0 mg) for 6 weeks to non-psychotic relatives in an open-label protocol (Tsuang et al., 1999b; Tsuang et al., 2002). Side effects were mild or mild to moderate, and were temporary. Five out of 6 subjects showed reduced negative symptoms and improved performance on a demanding test of sustained vigilance.

More recently, Rybakowski et al employed similar diagnostic criteria to identify schizotaxia in 7 adult, non-psychotic, non-schizotypal first- or second-degree biological relatives of patients with schizophrenia (Rybakowski et al., 2007). These subjects (aged 17–44 years old) reported a decline in social or occupational functioning over the previous year, and neuropsychological problems. All subjects took low doses of risperidone (0.5 – 2.0 mg) for 3–7 years. Similar to our results, all 7 subjects demonstrated improvements in negative symptoms and neuropsychological functions, and also showed improvement in social and vocational function. Consistent with these findings, Koenigsberg et al administered risperidone (up to 2.0 mg) to 25 patients with DSM-IV schizotypal personality disorder for 9 weeks in a double-blind, placebo-controlled study and documented significant reductions in both positive and negative symptoms (Koenigsberg et al., 2003).

The goal of the current study is determine whether neuropsychological, clinical, social or medical abnormalities are amenable to attenuation in adult subjects classified as schizotaxic. The current study extends previous efforts to modify symptoms of schizotaxia by administering low doses of risperidone to adult non-psychotic relatives in a double-blind, placebo-controlled design to control for expectation and other biases that are inherent in open-label trial protocols. This study is part of a larger project (the ‘Changsha’ study) that was conducted in Changsha, Hunan Province, China that sought to both identify and validate a syndrome of schizotaxia, and to remediate its symptoms (Stone et al., in press). We hypothesized that relatives with schizotaxia who received low doses of risperidone would show milder cognitive deficits, milder negative symptoms and less self-reported social dysfunction than relatives with schizotaxia who received placebo.

Methods

Overview

Relatives were recruited into ‘Phase I’ of the study first, which was an evaluative phase to determine whether they met criteria for schizotaxia. Subjects who met diagnostic criteria for schizotaxia were recruited subsequently into ‘Phase II’, which included the double-blind, 6-week treatment trial of risperidone or placebo control. Inclusion/exclusion criteria for Phase I thus included several items related to possible risperidone treatment in Phase II. Details of the recruitment and assessment of subjects for Phase I are described elsewhere (Stone et al., in press), and will be summarized briefly here.

Subjects

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 other psychiatric hospitals in Hunan Province. All subjects provided informed consent as a condition of their participation and received financial remuneration for their time. Subjects who met diagnostic criteria for Phase I were recruited for Phase II of the study.

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: 1) have an estimated IQ below 80; 2) have a lifetime history of a psychotic disorder (assessed with the modules from the Diagnostic Interview for Genetic Studies); 3) have a substance abuse diagnosis within 6 months of entry into the study; 4) have a head injury with documented loss of consciousness exceeding 5 minutes (or subsequent cognitive deficits); 5) have a history of neurologic disease or damage; 6) have a medical condition with significant cognitive sequelae; 7) have a history of electroconvulsive treatment; 8) be pregnant or nursing (women only); 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; and 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 were based on negative symptoms and/or neurocognitive dysfunction, as proposed previously (Stone et al., in press; Tsuang et al., 1999b). Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). 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) to meet the negative symptom criterion.

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 to include criterion measures for which Chinese versions of the tests were available, and for most measures, versions of tests for which normative data were available for Chinese subjects. The neurocognitive measures included tests of: 1) vigilance/working memory, using a Chinese version of the Stroop Test, Color-Word condition, and the Digit Span test from the Wechsler Adult Intelligence Scale – Revised, Chinese version; 2) verbal memory, using the 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 despite the unavailability of Chinese sample norms because it uses visual, nonverbal stimuli (instructions were given in Chinese), adequate norms were available for American samples, and it has been included in other Asian studies of schizophrenia (Goto et al., 2009). Criterion measures included Total Errors and Total Perseverative Errors.

Levels of cognitive deficits required to meet provisional criteria were set initially at the same levels as those required in our pilot study. Those levels were relatively stringent so as to reduce false positive cases and to attain a percentage of cases that we observed previously to show core cognitive features of schizotaxia (about 20–50%) (Faraone 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. They also required deficits in a second cognitive domain that equaled or exceeded 1 standard deviation below the expected mean. The utilization of these criteria using the modified battery of tests, however, resulted in the classification of far fewer relatives than we obtained in the earlier

pilot 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. The revised criteria also stipulated that subjects could meet criteria for schizotaxia if they met the negative symptom criterion alone. As a result of this change, 86/189 (46%) relatives met the modified initial criteria 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 et al., 1994) that covered psychosis. The Structured Interview for Schizotypy (Kendler et al., 1989) was used to assess for the presence of schizotypal personality disorder and for the presence of positive and negative symptoms. These data are not yet available for analysis and will be reported separately. The subjects also received clinical interviews and rating scales in addition to tests and ratings for schizotaxia. These additional measures 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 social 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 criteria for schizotaxia were evaluated. Both the GAF and the SAS were used as independent measures of clinical and social function to validate differences between relatives who did and did not meet our preliminary operational criteria for schizotaxia (Stone et al., 2001). Subjects also received the Symptom Checklist 90 – Revised (SCL-90-R), which is another self-report questionnaire (Derogatis, 1993). Results from that measure will be reported separately.

Supplemental Cognitive Assessment

In addition to the cognitive diagnostic criteria for schizotaxia, additional cognitive tests were administered (Stone et al., in press). Effects of risperidone on performance on these measures will also be reported separately.

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. Subjects in Phase II were also assessed for abnormal movements using the Abnormal Involuntary Movement Scale, the Barnes Akathisia Scale and Simpson-Angus Rating Scale. Medical assessments were also administered to determine general health and vital signs. No individuals were excluded because of medical criteria. Medical data will be analyzed further in a separate study.

Phase II Recruitment

Subjects who met diagnostic criteria for schizotaxia and the other inclusion criteria for participation in the study were recruited. Of the 86 relatives who met our revised diagnostic criteria, 54 (63%) provided initial consent to enter the double-blind protocol, but 16 withdrew their consent before receiving any medication, and 2 subjects withdrew from Phase II within the first 2 weeks (their data were not included in subsequent analyses). The remaining 36 subjects (42%) agreed to enter the double-blind protocol for a 6-week course of risperidone or placebo. Data were collected for this study from December 2006 to December 2008.

To assess treatment sample representativeness, we conducted mean group comparisons between the obtained treatment group and the subsample of relatives with putative schizotaxia who did not participate in treatment. There were no between-group differences on demographic variables (e.g., age, education, gender); however, significant differences emerged on clinical and some cognitive variables. Specifically, the treatment subsample of schizotaxic relatives showed a higher negative symptom load as indexed by both the total SANS score ($F=5.7$, $p < 0.02$) and the number of SANS items scored greater than 3 ($F=8.2$, $p=0.005$). Not surprisingly, the treatment subsample also demonstrated a significantly lower GAF ($F=14.2$, $p < 0.001$). While there was no difference on most cognitive variables, two differences did emerge, but were mixed: the treatment subsample showed less interference on the Stroop Color-Word Test ($F=5.7$, $p < 0.02$), but on average made a greater number of perseverative errors on the WCST ($F=12.1$, $p=0.001$).

Risperidone Administration

Upon entry to Phase II of the study, subjects were assigned randomly to the risperidone or placebo conditions by the study pharmacist based on a random number algorithm. The pharmacist was not an investigator on the study and was not involved in any other phase of the protocol. None of the investigators/raters knew which subjects received risperidone and which subjects received the placebo. As a backup, the pharmacist sent the code to one of the investigators in Boston (WSS), who unsealed the blind after the data collection phase ended and all data were entered into the database.

Risperidone and placebo were administered in liquid form for 6 weeks. Most subjects mainly received the medication or placebo at the hospital (31/36), while a few received it delivered to their homes by study staff (5/31). Doses of risperidone began at 0.25 mg and increased to the maximum of 2.0 mg in the first 1–2 weeks in all active-treatment subjects. Side effects were mild and mainly subsided over time, as shown in Table 1. Six out of 20 subjects who received risperidone reported side effects, with 3/6 reporting headaches. Two out of 16 subjects who received placebo also reported side effects. No subject required or requested a lower dose after reaching 2.0 mg, although one subject stopped taking the medication 2 days before the end of the study in part because of reported weight gain (data from that subject were included in subsequent analyses). After 6 weeks, subjects were retested while still on the medication, on clinical, neuropsychological, and medical measures.

Data Assessment

Group differences—These analyses focused on group differences between relatives with schizotaxia who received a course of risperidone in a double-blind protocol, and those who received a placebo. 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—In our previous study (Stone et al., in press), we used a cluster analysis to assess the validity of dividing relatives into two distinct subgroups based on our diagnostic criteria (i.e., those with schizotaxia and those without schizotaxia). The results of the cluster analysis showed that some subjects who were classified as meeting criteria for schizotaxia would be better classified as belonging to the non-schizotaxic group. Consequently, we assessed effects of risperidone on subjects using our original diagnostic criteria and also using the cluster-derived groups. Since some subjects were removed from the schizotaxia group after the cluster analysis, the number of subjects in these latter analyses is smaller.

Concordance between the criterion- and cluster-derived membership of the non-schizotaxic and schizotaxic groups was good. Only subjects from the conceptually-derived schizotaxic group were re-assigned to the non-schizotaxic group in the cluster analysis. No member of the criterion-derived non-schizotaxic group became a member of the schizotaxic group. More specifically, the putative schizotaxic relative group was decreased by eliminating relatives formerly included in the conceptually-derived schizotaxic group who demonstrated cognitive deficits but a lower load of negative symptoms (see Stone et al., in press). The cluster analysis sorted subjects in a manner that strengthened the membership of the schizotaxic group by maximizing between group differences and minimizing within group differences, an endpoint that could not be achieved in the conceptually driven criterion-based method.

Statistics

Group differences—Baseline statistical differences between the study groups were tested using an independent samples *t*-test for continuous variables and a Chi-Square test for the categorical variable, gender. Multiple mixed between-within subjects (repeated measures) analysis of covariance (ANCOVA) tests were conducted to explore the impact of experimental treatment on the dependent variables; age and gender were used as covariates, as in our earlier analyses. Education, which differed between groups in the earlier study, did not differ significantly between the subsets of subjects who participated in the current study. Moreover, analyses run with and without education as a covariate produced similar results. Consequently, education was not used as a covariate in the final analyses. The two independent variables included the between-subjects variable (treatment: low dose risperidone or placebo) and within-subjects variable (time: baseline and post-intervention). The main effects for each independent variable and interaction effect were examined for significance with an alpha level of .05; there was no correction for multiple tests. Effect sizes were calculated based on unadjusted post-intervention group means using Cohen's *d* (Cohen, 1988).

Cluster Analyses—We conducted a hierarchical cluster analysis with SPSS Version 16 (SPSS, 2208) using squared Euclidean distance on seven measures (negative symptom load (i.e., SANS), 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. Additional details of the procedure were described previously (Stone et al., in press).

Study Design and Quality Assurance Procedures

As noted, data was collected at the Changsha site. 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. These assessments were repeated following the completion of the double-blind protocol.

Before the study began, multiple training sessions, including training in scientific research ethics, were held in Changsha to train site investigators in the protocol and associated procedures. American investigators conducted yearly site visits 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 last two years of the study. One of the investigators in Boston, who was both a clinical psychologist and 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

Demographic differences

Table 2 shows demographic information for schizotaxia subjects. Using the modified initial criteria, 36 subjects were recruited into the study. Sixteen of these subjects were randomized to the placebo control group and 20 were randomized to the risperidone group. The two groups did not differ significantly in age, gender or level of education. Using the cluster-derived groups resulted in 11 fewer subjects classified with schizotaxia. Of these, 10 were in the placebo control group and 15 were in the risperidone group. The composition of these groups also did not differ significantly in age, gender or level of education.

Treatment effects using the (modified) initial criteria for schizotaxia

Table 3 shows effects of placebo and risperidone administration, using subjects who met the modified initial criteria. Data are presented for criterion neurocognitive and negative symptom measures, and for additional measures of social (SAS Total score) and clinical (GAF and SANS Total scores) function. Baseline clinical and neurocognitive characteristics did not differ significantly between the risperidone and the placebo groups for either the initial or the cluster-derived samples (described below); however, the initial criteria risperidone group showed a trend ($p=0.76$) toward higher SANS scores rated 3 or higher. Levels of several neurocognitive (WAIS-R Digit Span, Logical Memory delayed recall, WCST Total Errors and Perseverative Errors T scores) and negative symptom (number of SANS scores rated 3 or higher) criterion measures, and two non-criterion clinical measures (GAF and SANS Total scores), improved significantly from baseline to the 6-week follow-up. In contrast, none of the main effects for group were significant.

Three variables, however, showed significant Group $\times$ Time interaction effects. Subjects who received risperidone showed significantly fewer WCST total errors and fewer perseverative errors than subjects who received placebo. The effect sizes of the difference between the risperidone and placebo groups at the 6-week follow-up were medium (0.53 and 0.71, respectively). Subjects in the risperidone group also showed better social function on the SAS, an independent, non-criterion measure of function, after 6 weeks than they did in the placebo group. The effect size was nearly in the medium range ($d = 0.46$). Other changes and between-group differences were not significant statistically.

Treatment effects using the (modified) initial criteria for schizotaxia

Table 4 shows effects of placebo and risperidone administration using subjects determined by the cluster analyses. Data are presented for the same criterion and non-criterion measures that are shown in Table 3. Analyses with the smaller sample showed a significant main effect for improvement over time in only one neurocognitive criterion measure (WCST Total Errors), though each measure improved nonsignificantly. The negative symptom (number of SANS scores rated 3 or higher) criterion measure and two non-criterion clinical measures (GAF and SANS Total scores) improved significantly from baseline to the 6-week follow-up, as they did using the larger sample. As before, none of the main effects for group were significant.

The same three variables showed significant Group $\times$ Time interaction effects using the cluster-derived groups. Subjects who received risperidone showed significantly fewer total errors and fewer perseverative errors on the WCST than subjects who received placebo after treatment. The effect sizes of the difference between the risperidone and placebo groups at the 6-week follow-up were larger in this sample, with one remaining in the medium range (0.65; WCST Total Errors T score) and one increasing to the large range (0.93; WCST Perseverative Errors T score). The effect size of the improvement in social function shown by the risperidone group on the SAS also increased from the small to the medium range (0.69). Comparisons of the positive effects of risperidone on WCST Perseverative Errors and on the SAS total scores are also shown visually in Figures 1 and 2, for both definitions of schizotaxia. The figures show significant improvement in these measures using either definition of the syndrome, with slightly (i.e. non-significantly) higher effect sizes in the (smaller) cluster-derived groups. Note that better performance on the WCST is denoted by increases in the risperidone group (Figure 1), while better function on the SAS is denoted by decreases in the risperidone group (Figure 2).

Discussion

Our previous study showed that a subset of non-psychotic, first-degree relatives of patients with schizophrenia demonstrated impairments in several measures of clinical, neurocognitive and social function, compared to a larger subset of relatives and to community comparison control subjects (Stone et al., submitted). Those findings supported the view that one or more liability syndromes for schizophrenia (i.e. 'schizotaxia') might be identified and defined provisionally with research criteria. This report extends those findings by providing evidence that a psychopharmacological intervention can attenuate at least some schizophrenia-related cognitive and social difficulties in non-psychotic relatives of patients with schizophrenia. In particular, administration of risperidone to schizotaxia subjects in a double-blind, placebo-controlled paradigm for 6 weeks resulted in fewer total and perseverative errors on the WCST, compared to schizotaxia subjects who received a placebo. Moreover, subjects who received risperidone endorsed higher levels of social and interpersonal function on the SAS, which was an independent measure of function that was neither a criterion measure for schizotaxia, nor in the same functional domain as the criterion measures. Notably, effect sizes for these three measures were in the small to moderate range initially, but increased to the medium to large range when membership in the schizotaxia group was determined by cluster analysis.

These findings confirm and extend two previous investigations that administered risperidone to adult subjects with schizotaxia using open-label designs. In one, 5 out of 6 subjects improved over a 6-week protocol on a demanding test of sustained vigilance, and showed modest reductions in negative symptoms (Tsuang et al., 1999b; Tsuang et al., 2002), while Rybakowski et al showed improvements over 3–7 years on cognitive and social measures of function (Rybakowski et al., 2007). The WCST was one of the measures that improved in

the Rybakowski et al study. Both studies capped the maximum dose of risperidone at 2.0 mg, as did the current study. The consistency of the current, double-blind, placebo-controlled findings with the previous open label ones minimize the likelihood that improvements in the risperidone group occurred primarily because of expectation of improvement, or because of practice effects. It is particularly notable that performance on the WCST, which was among the tests most susceptible to practice, improved to a significantly greater degree in the risperidone group than in the placebo group. The failure to demonstrate reductions in negative symptoms or other neurocognitive functions under controlled conditions, however, does raise the issue of both practice effects and / or expectation in the open-label investigations. This possibility is emphasized by the significant improvements in negative function and in several neurocognitive functions between the baseline and follow-up assessments, in both the risperidone and the placebo groups.

The positive effects of risperidone on some but not most measures of cognition also occurred in our previous investigation. The improvement in the WCST, a test sensitive to executive function, differed from the improvement in sustained vigilance in the previous study. In some ways, the narrow range of neurocognitive improvement is unexpected. There is considerable evidence that beneficial effects of antipsychotic medications on cognition in schizophrenia act on a broad range of cognitive functions in schizophrenia, although typically with small effect sizes (Cuesta et al., 2001; Houthoofd et al., 2008; Keefe et al., 2007a; Keefe et al., 2007b; Woodward et al., 2005).

There are several possible reasons for this discrepancy. One involves the manner in which subjects can meet the cognitive criterion for schizotaxia. In both the previous and current studies, not all subjects showed deficits in the same measures or cognitive domains. Consequently, average group values in the current study were not as impaired as they would be if all subjects were selected for deficits in the same areas. This approach limits the possible range of effect produced by interventions such as risperidone. One way to minimize the effects of cognitive heterogeneity in schizotaxia in the future would be to utilize neurocognitive composite scores that combine scores from individual measures, and which are often used in studies of schizophrenia (Keefe et al., 2007a; Kremen et al., 2004).

A second possible reason for demonstrating a more limited range of cognitive effects on subjects with schizotaxia than on subjects with schizophrenia involves the short period of risperidone administration. Most trials of antipsychotic medications are longer than 6 weeks. The CATIE study assessed cognitive effects after 8 and 12 weeks of treatment, for example, but also after 12 and 18 months (Keefe et al., 2007a). It is possible that risperidone administration would have had led to broader improvement if the trial was longer. Similarly, the failure of risperidone to significantly reduce negative symptoms might partly reflect the short duration of treatment. Although longer trials may complicate recruitment efforts in studies of schizotaxia, they merit consideration in future studies.

A third possible reason for the heterogeneous response to risperidone involved the sample size. Particularly when the cluster-derived groups were used for the analyses, the sample was small, and may have lacked the necessary statistical power to detect small differences. Nevertheless, it is significant that in the cognitive areas in which risperidone was effective, it produced medium to large effect sizes using the cluster-derived groups, and did so in a short period of time. Risperidone's moderate-sized positive effects on social function are generally consistent with small effects of antipsychotic medications on the social subscales of the Heinrich-Carpenter Quality of Life Scale in the CATIE study (Keefe et al., 2007b), and with modest improvement on an emotion perception test utilized in the same study (Penn et al., 2009).

A fourth reason to explain the limited effects of risperidone on cognition does not focus on methodological problems, but on the inherent limits of the drug's effectiveness in remediating cognitive and other symptoms of schizotaxia. The consistency of its positive but limited cognitive effects in the current study with its positive but also limited effects in our open-label investigation (albeit in a different cognitive domain) denote its ability to attenuate some but not most cognitive deficits in schizotaxia. These effects underscore a point made in our earlier report (Tsuang et al., 1999b), which is that the positive effects we observed in this study do not currently provide sufficient justification to administer risperidone clinically to non-psychotic relatives.

Related to this issue, and in addition to the points raised about the relatively small samples sizes (especially for the cluster-derived groups), heterogeneous clinical criteria and short length of the risperidone trial, another limitation of the current study should be noted. Although there is some validation for the criteria used to classify schizotaxia in this and previous studies, we stress that these criteria are highly provisional at this point, and are subject to change. The slightly different findings obtained using the modified original criteria or the cluster-derived criteria demonstrate this point and the need for further validation and investigation of the proposed syndrome. As the specific criteria evolve, their amenability to remediation will also require re-evaluation.

Despite these limitations, the current results are encouraging, and support the view that some characteristic problems of schizophrenia-spectrum disorders might be amenable to attenuation in non-psychotic adult relatives. Moreover, they add to a growing, multidimensional repertoire of possible methods to attenuate the liability for schizophrenia in high risk subjects. Whether or not attenuation of neurocognitive or other deficits/abnormalities can alter a trajectory to schizophrenia is an empirical question that has yet to be answered. It remains essential to identify the individuals who are at highest risk for psychosis, which is an endeavor that remains difficult (Dazzan et al., 2004). In this context, it is notable that subjects with greater levels of at least some clinical symptoms (i.e. negative symptoms) preferentially agreed to enter the treatment trial in this study, which raises the possibility that individuals with these levels of impairment (and who are not psychotic) may be particularly amenable to intervention efforts. It also highlights the need for future studies of schizotaxia to assess a broader range of clinical symptoms, such as positive symptoms and subjective experiences. In the meantime, incremental attempts to define and modify symptoms of liability in well-controlled studies are likely to facilitate progress towards viable strategies for early intervention.

Ethical Statement

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.

Acknowledgments

The authors wish to acknowledge the generous and professional assistance of the staff at the Mental Health Institute at the Second Xiangya Hospital, Central South University, in Changsha, China, in recruiting and testing research subjects. We also wish to acknowledge the subjects who agreed to participate in the study.

Role of Funding Source

This study was supported in part by Ortho-McNeil Janssen Scientific Affairs, LLC, and by National Institute of Mental Health Grant RO1-MH065562 (COGS; Consortium on the Genetics of Schizophrenia). These sources had no further role in determining the study design, data analyses or preparation of the manuscript

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Figure 1.

Effects of risperidone on Wisconsin Card Sorting Test performance. The figure shows significant time $\times$ group interactions using initial conceptual (left side of figure) and cluster-derived (right side of figure) groups, with the risperidone group showing significant improvement after treatment versus the placebo control group. Higher scores denote better cognitive performance.

Figure 2.

Risperidone effects on self-reported Social Adjustment Scale total score. Time $\times$ group interactions were significant using conceptual (left side of figure) and cluster-derived (right side of figure) criteria, with the risperidone group showing significant improvement after treatment versus the placebo control group. Lower scores denote better social function.

Table 1

Non-serious side effects reported by individual subjects in the risperidone and in the placebo conditions

Non-Serious Adverse Events					
Treatment Condition	Side Effects	Effect Duration (days)	Severity	Action Required	Outcome
Placebo *	Insomnia	4	Mild	None	Resolved
Placebo	Weight Gain	14	Mild	None	Resolved
Risperidone **	Headache	18	Mild	None	Resolved
Risperidone	Headache	3	Mild	None	Resolved
Risperidone	Dry Mouth	21	Mild	None	Resolved
Risperidone	Drowsy	7	Mild	None	Resolved
Risperidone	Weight Gain	21	Mild	None	Resolved***
Risperidone	Headache	5	Mild	None	Resolved

* n=16

** n=20

*** Subject dropped out of the study 2 days before completion of the protocol

Table 2

Demographic variables for risperidone and placebo schizotaxia groups defined by (modified) initial criteria and by cluster analyses¹

Basis of Schizotaxia Group Definition	Initial Criteria		Cluster Derived	
	Placebo (n=16)	Risperidone (n=20)	Placebo (n=10)	Risperidone (n=15)
Age ²	35.6 (10.5)	32.2 (12.1)	31.2 (8.9)	27.3 (9.7)
Gender N (% Male)	9 (56.3%)	11 (55.0%)	6 (60.0%)	9 (60.0%)
Personal Education	11.7 (2.8)	12.3 (2.5)	12.2 (3.1)	12.8 (2.6)

¹ Expressed as means ($\pm$ standard deviations) for age and education; gender is expressed as frequencies with percentages in parentheses.

² Independent samples *t*-test statistic for continuous variables; Chi-Square was used for gender.

Table 3

Group performance on criterion and non-criterion variables using (modified) initial criteria for schizotaxia with mixed between-within (repeated measures) ANCOVAs^{1,2,3,4,5}

	Placebo (n=16) M (SD)		Risperidone (n=20) M (SD)		Time Effect <i>F</i> -Statistic, <i>p</i>	Between Subjects Effect <i>F</i> -Statistic, <i>p</i>	Time × Group Interaction Effect <i>F</i> -Statistic, <i>p</i>	Follow-Up Placebo- Risperidone Effect Sizes ⁶
	Baseline	Follow- Up	Baseline	Follow- Up				
Neurocognitive Criterion Variables								
Digit Span ScS ⁴	11.9 (2.7)	12.6 (2.3)	12.2 (2.3)	13.4 (2.3)	F=7.98 p=0.008	F=0.379 p=0.542	F=0.277 p=0.602	-0.35
Stroop Color-Word RS ⁵	31.2 (6.5)	37.0 (14.3)	33.7 (12.7)	36.5 (11.7)	F=2.01 p=0.166	F=0.007 p=0.932	F=0.902 p=0.349	0.04
LM Delayed Recall ScS ⁵	7.4 (3.4)	10.6 (5.5)	8.9 (5.6)	11.8 (6.0)	F=5.35 p=0.027	F=0.448 p=0.449	F=0.162 p=0.69	-0.21
LM Savings Score (%) ⁵	80.4 (19.4)	81.0 (25.6)	79.5 (31.7)	80.9 (22.9)	F=0.082 p=0.777	F=0.90 p=0.766	F=0.001 p=0.975	0.004
WCST Total Errors T- Score ⁵	40.8 (14.1)	41.8 (15.0)	40.9 (10.9)	49.2 (12.8)	F=5.23 p=0.029	F=0.235 p=0.631	F=4.20 p=0.049	-0.53
WCST Perseverative Errors T- Score ⁵	45.1 (17.4)	43.7 (17.1)	45.4 (13.9)	56.6 (19.0)	F=4.84 p=0.035	F=0.698 p=0.410	F=9.22 p=0.005	-0.71
Negative Symptom Criterion Variable								
SANS Ratings ≥ 3 ⁴	3.8 (2.9)	1.9 (1.9)	5.5 (3.1)	2.1 (1.9)	F=31.55 p<0.001	F=0.635 p=0.432	F=2.44 p=0.128	-0.11
Clinical / Social Function Non-Criterion Variables								
SAS	70.0 (17.9)	77.8 (23.6)	72.5 (21.2)	67.4 (21.2)	F=0.545 p=0.466	F=0.092 p=0.763	F=4.79 p=0.036	0.46
GAF	67.7 (8.6)	70.6 (7.7)	63.6 (7.1)	67.6 (6.9)	F=10.76 p=0.003	F=1.214 p=0.279	F=0.396 p=0.533	0.41
SANS Total Score	35.1 (12.3)	31.1 (9.4)	40.2 (10.7)	33.0 (10.4)	F=14.22 p=0.001	F=0.470 p=0.498	F=0.907 p=0.348	-0.19

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

² Sample sizes are based on an overall $n = 36$, with 1, 32 df, with age and gender as covariates.

³ Higher scores denote better performance for all neurocognitive variables and for GAF; higher SANS and SAS scores denote more severe symptoms or reduced social functioning, respectively.

⁴ ScS=Scaled Score; RS=Raw Score; LM=Logical Memory; WCST=Wisconsin Card Sorting Test; SANS=Scale for the Assessment of Negative Symptoms; SAS=Social Adjustment Scale Total Score; GAF= Global Assessment of Functioning Scale; ns=not significant.

⁵ Significant p values are bolded.

⁶ Effect size estimates are based on Cohen's d using post-intervention group raw score means and the pooled standard deviation.

Table 4

Group performance on criterion and non-criterion variables using cluster-derived schizotaxia groups, with mixed between-within (repeated measures) ANCOVAs^{1,2,3,4,5}

	Placebo (n=10) M (SD)		Risperidone (n=15) M (SD)		Time Effect	Between Subjects Effect	Time × Group Interaction Effect	Follow-Up Placebo- Risperidone Effect Sizes ⁶
	Baseline	Follow- Up	Baseline	Follow- Up				
Neurocognitive Criterion Variables								
Digit Span Scs ⁴	11.4 (3.1)	12.8 (2.5)	12.1 (2.5)	13.6 (2.5)	F=1.93 p=0.179	F=0.330 p=0.572	F=0.157 p=0.696	−0.32
Stroop Color-Word RS ⁵	34.3 (5.0)	41.4 (16.0)	37.1 (12.8)	39.8 (10.2)	F=2.22 p=0.151	F=0.002 p=0.962	F=1.12 p=0.305	0.12
LM Delayed Recall Scs ⁵	6.9 (3.4)	11.8 (5.5)	9.9 (5.4)	12.9 (6.1)	F=2.20 p=0.153	F=0.929 p=0.608	F=1.14 p=0.297	−0.19
LM Savings Score (%) ⁵	77.2 (17.1)	87.2 (16.2)	83.9 (27.7)	84.4 (17.7)	F=1.57 p=0.224	F=0.003 p=0.957	F=0.278 p=0.604	0.17
WCST Total Errors T- Score ⁵	43.3 (15.9)	43.2 (17.6)	43.0 (11.2)	52.9 (11.8)	F=5.05 p=0.035	F=0.263 p=0.614	F=6.31 p=0.020	−0.65
WCST Perseverative Errors T- Score ⁵	47.3 (14.4)	44.8 (19.5)	48.3 (14.4)	62.1 (17.5)	F=3.44 p=0.077	F=0.961 p=0.338	F=11.73 p=0.003	−0.93
Negative Symptom Criterion Variable								
SANS Ratings ≥ 3 ⁴	6.0 (0.67)	3.0 (1.8)	7.0 (1.6)	2.5 (1.9)	F=10.09 p=0.005	F=0.244 p=0.626	F=2.19 p=0.154	0.27
Clinical / Social Function Non-Criterion Variables								
SAS	74.5 (18.7)	82.9 (26.7)	73.5 (24.4)	65.2 (24.5)	F=0.148 p=0.704	F=0.198 p=0.661	F=4.34 p=0.050	0.69
GAF	62.6 (5.8)	67.0 (6.7)	60.3 (3.9)	64.9 (4.9)	F=6.17 p=0.022	F=0.86 p=0.364	F=0.013 p=0.912	0.36
SANS Total Score	42.5 (8.3)	35.7 (8.8)	44.9 (6.5)	36.2 (9.7)	F=5.83 p=0.025	F=0.203 p=0.498	F=0.157 p=0.696	−0.06

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

² Sample sizes are based on an overall $n = 25$, with 1, 21 df, with age and gender as covariates.

³ Higher scores denote better performance for all neurocognitive variables and for GAF; higher SANS and SAS scores denote more severe symptoms or reduced social functioning, respectively.

⁴ ScS=Scaled Score; RS=Raw Score; LM=Logical Memory; WCST=Wisconsin Card Sorting Test; SANS=Scale for the Assessment of Negative Symptoms; SAS=Social Adjustment Scale Total Score; GAF= Global Assessment of Functioning Scale; ns=not significant

⁵ Significant p values are bolded.

⁶ Effect size estimates are based on Cohen's d using post-intervention group raw score means and the pooled standard deviation.