Thought Disorder in Offspring of Schizophrenic Parents: Findings From the New York High-Risk Project

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The goal of the present analyses was to examine the hypothesis that mild forms of thought disorder (TD) may serve as an indicator of genetic liability for schizophrenia. A subset of 232 subjects drawn from the New York High-Risk Project was used to compare individuals at high risk for schizophrenia (ie, offspring of parents with schizophrenia; n = 63) with 2 groups of individuals at low risk for schizophrenia (ie, offspring of parents with affective disorder [n = 52] and offspring of psychiatrically normal parents [n = 117]). Subjects were administered the Rorschach Inkblot Test, and their responses were assessed according to the Thought Disorder Index (TDI). The high-risk offspring displayed significantly more TD than the other 2 groups, as shown by significantly higher TDI scores. Moreover, they had more deviant verbalizations, according to their significantly higher scores on a composite Idiosyncratic Verbalizations score. As expected, the offspring who developed psychosis produced more TD in adolescence than those who did not develop psychosis. In the sample as a whole, TD scores during late adolescence/early adulthood were positively associated with schizotypal features during mid-adulthood. These findings support the assertion that the presence of TD serves as an endophenotypic marker of a schizophrenia diathesis.

Key words: schizophrenia/endophenotype/genetic liability/psychosis/schizotypal features

Introduction

The study of individuals considered to be at heightened risk for schizophrenia based on their relationship with an affected person is a particularly useful strategy for examining the efficacy of test measures as possible indicators of a genetic diathesis. This article reports on a measure presented in the New York High-Risk Project (NYHRP), a longitudinal prospective study in which initially unaffected and untreated offspring of schizophrenic parents, parents with major affective disorders, and parents without such disorders were followed from mid-childhood through mid-adulthood.1 Major goals of the NYHRP as a whole were to identify neurobiological and other types of deficits as likely predictors and to establish some of these deficits as endophenotypes indicating genetic liability.2,3 As subjects in the NYHRP are past the peak risk ages and approximately 14% of the high-risk subjects have developed schizophrenia or related psychoses, it is now possible to consider the predictive as well as endophenotypic status of a broad range of the variables assessed at earlier ages. Several predictors, probably reflecting genetic susceptibility to schizophrenia, have already been demonstrated among measures in the NYHRP, including attentional dysfunction, comparatively poor working memory, and disruptions in gross motor performance.3

This report focuses on examining thought disorder (TD) as a potential endophenotype of schizophrenia. Since Kraepelin4 and Bleuler5, TD has been considered one of the cardinal features of schizophrenia and a primary symptom reflecting the disease process itself. Meehl6,7 has maintained that TD is not only core to schizophrenia but also a reflection of the genetic liability to the illness. The term “formal TD” refers to disturbances or disruptions in the manner or mode of thinking, concentrating, attending, or reasoning.8 In its milder form, it is referred to as cognitive slippage.6,7
Both clinicians and researchers have noted that TD is a nonspecific feature observed in various psychotic disorders. Although the quantity of TD does not distinguish among the psychotic disorders, the quality of TD differs among different disorders. For example, Holzman et al differentiated characteristic features of schizophrenic and manic TD. Schizophrenic TD is characterized by combinatory thinking, confusion, and idiosyncratic verbalizations, whereas manic TD is characterized by inappropriate flippancy and elaborate, playful confabulations. In addition, TD in schizophrenia appears to be a more trait-related feature of the disorder.\textsuperscript{11,14}

Family Studies of Thought Disorder

Clinically unaffected first-degree relatives of schizophrenic patients exhibit significantly more TD than healthy controls.\textsuperscript{15–17} A study of TD in extended pedigrees of 6 schizophrenic patients, with at least 2 affected family members,\textsuperscript{18} also indicated that TD aggregates in families; relatives with schizophrenia spectrum disorders (ie, schizophrenia or a Cluster A diagnosis) had significantly higher TD scores than family members with other mental illnesses or no mental illness.

The familial pattern of TD could reflect environmental as well as genetic factors. Whether TD has a heritable component can be determined by twin and adoption studies, and both types of investigations offer evidence supporting heritability. Comparative studies of monozygotic and dizygotic twins suggest that TD is heritable in normal individuals\textsuperscript{19} as well as in schizophrenia.\textsuperscript{20,21} In an investigation of referential communication disturbances in discordant twin pairs from the Maudsley twin study,\textsuperscript{2} the nonschizophrenic monozygotic co-twins showed a significantly higher frequency of missing references than their dizygotic counterparts. Kinney and colleagues\textsuperscript{22} observed that schizophrenic adoptees had significantly greater TD scores than adopted controls, and their biological relatives produced significantly more TD than the biological relatives of the controls. Furthermore, the biological relatives of schizophrenic adoptees, who shared genetic risk but not environmental risk with the probands, had significantly higher Thought Disorder Index (TDI) scores than the adoptive relatives. Meeth\textsuperscript{2,7} maintained that indices of mild TD (referred to as cognitive slippage) reflect a genetic liability for schizophrenia.

High-Risk Studies of Thought Disorder

Investigations of the offspring of schizophrenic parents have assessed TD using diverse methods. In the Copenhagen High-Risk Study, Griffith et al\textsuperscript{23} reported that while high-risk adolescents and young adults displayed more deviant associations and more idiosyncratic responses to word association tests than did low-risk controls, the number of deviant responses on these tests did not differentiate the high-risk subjects who later developed schizophrenia from the remainder of their group. When Parnas et al\textsuperscript{24} examined the same subjects on an adjective checklist instead of the word association test, the preschizophrenic subjects showed more “incoherence” and “pathology of associations” than other high-risk subjects or normal controls. Neither report\textsuperscript{23,24} fully described the TD items, rendering replication difficult.

Investigators in the Stony Brook High-Risk Project\textsuperscript{25} reported that offspring at risk for schizophrenia, responding to Thematic Apperception Cards using Rochester and Martin’s\textsuperscript{26} cohesion and reference pattern measures, exhibited the most deviance across several areas of speech compared with the other offspring groups, and had patterns of linguistic deviance similar to those observed in adult schizophrenia patients, though less severe. Offspring of bipolar or unipolar parents made significantly fewer ambiguous references than offspring of schizophrenic parents but more than the offspring of normal parents.

Arboleda and Holzman\textsuperscript{27} compared the quantity of TD in psychotic hospitalized, nonpsychotic hospitalized, high-risk, and normal children, based on verbatim responses to the Rorschach. Using Holzman’s TDI to score the responses, they found that high-risk and psychotic hospitalized children produced significantly more TD than the children in the other 2 groups. Total TDI scores of the high-risk and psychotic groups were equivalently elevated; the high-risk children’s TD, specifically, their tendency to produce incoherent,fluid, or autistic responses, was “strikingly similar” to that of the psychotic hospitalized children.

In an Israeli study, Arbelle et al\textsuperscript{28} rated formal TD from responses to a story game using the Kiddie Formal Thought Disorder Rating Scale (K-FTDS\textsuperscript{29}). Arbelle et al. were the only investigators to report no significant differences between the offspring of schizophrenic, other mental illness, and no mental illness parent groups. Low base rates of total formal TD were seen in all 3 groups. These investigators also found no significant difference in formal TD by offspring adulthood diagnosis. However, one limitation of the study is its reliance upon the K-FTDS,\textsuperscript{29} which, with only 4 items, provides less comprehensive assessment of TD than other measures and may be less sensitive to measuring more subtle forms of TD. Another study limitation is the categorization of the offspring adulthood diagnoses, in which borderline personality was included as part of the schizophrenia spectrum group, while affective disorders and anxiety disorders were combined into a single diagnostic outcome group, namely “internalizers.” These classification decisions may have obscured any real differences in TD by diagnostic outcome groups that may have existed.

In the Finnish Adoption Study, Wahlberg et al\textsuperscript{30} used the TDI to score the Rorschach responses of clinically
If, as Meehl6,7 asserted, cognitive slippage serves as a phenotypic indicator of an underlying integrative neural defect (“schizotaxia”) that characterizes individuals with a heightened liability for developing schizophrenia, then offspring of schizophrenic parents as a group would be expected to show greater levels of cognitive slippage. However, it is possible that only certain types of cognitive slippage, such as combinatorial thinking or idiosyncratic thinking, are endophenotypic markers of liability. The present report from the NYHRP aims to explore the status of TD as an indicator of genetic susceptibility to schizophrenia by comparing TD in offspring at risk for schizophrenia or for affective disorder or at low risk for these disorders (normal comparison offspring). Thus, the goals of these analyses are 2-fold: (a) to determine whether patterns of TD differ among the offspring of the different parental groups and (b) to determine whether premorbid TD is related to clinical outcome in later adulthood. The present analyses add to our current knowledge regarding the relationship between TD and schizophrenia liability in several ways. First, the NYHRP continued follow-ups of its offspring beyond the period of highest risk. Inclusion of 2 cohorts (Samples A and B of the NYHRP) results in a large sample size and therefore permits greater statistical examination of a definitive association between TD and genetic risk for schizophrenia than many of the other studies. The NYHRP sample also permits comparison of individuals at risk for schizophrenia with a group at risk for other psychiatric disorders, which is lacking in some studies. Finally, individuals at high- and low-risk for schizophrenia are compared here in terms of both global and specific indices of TD.

The Present Report

Methods

Participants

The participating families consisted of a subset of the 2 independent samples (A and B) of the NYHRP, each sample consisting of offspring of schizophrenic, affectively ill, and psychiatrically normal parents (the High Risk for Schizophrenia [HRSz], High Risk for Affective Disorder [HRAf], and normal control [NC] offspring groups, respectively). All offspring were Caucasian, English speaking, and free of mental retardation, major psychiatric disorders or treatment for emotional problems at recruitment in 1971–72 (Sample A) or 1977–79 (Sample B) at ages 9.5 ± 1.7 or 9.0 ± 1.8 (mean ± SD), respectively. Follow-up of both samples has included 7 rounds of examinations, approximately 3 years apart. Details of the recruitment procedures, parental diagnoses, and longitudinal follow-up have been presented elsewhere.1,31,32 After complete description of the study, written informed consent was obtained from the parents for themselves and their children at each testing round and individually from the children after reaching age 18. Institutional Review Board approval was obtained for each phase of the NYHRP.

Assessment of Formal Thought Disorder

A 4-card Rorschach test33 was administered in round 4 (mean ages 20.29 ± 1.90, Sample A, and 18.56 ± 2.13, Sample B) following procedures described by Rapaport et al.34 The 4-card version of the Rorschach consisted of 1 red and black card, 2 achromatic cards, and 1 color card. Prior research35 indicates that this shortened version yields comparable results as the full 10-card set in terms of quantity and quality of TD. Individuals’ responses to the Rorschach were audiotaped and subsequently transcribed verbatim for scoring using the TDI.36,37 Both test administration and scoring were performed by investigators who were naive in terms of parental diagnostic group and adulthood diagnosis of the offspring.

The TDI can be used to provide a quantitative index of the amount and severity of disordered thinking and to characterize qualitative features of TD. It includes 23
categories of cognitive slippage, ranging from 0.25 (very mild) to 1.0 (reflecting the most severe). Examples of mild TD include peculiar word usage and incongruent word combinations. The more severe end of the disordered thought spectrum includes autistic logic, neologisms, and incoherence. Readers are referred to the scoring manual36,37 for a complete description of the categories.

Two raters with extensive experience in the administration and scoring of the TDI (M.J.C. and M.E.S.) independently scored the transcribed protocols according to the revised manual.37 Consensus scores were subsequently assigned. The psychometric properties of the TDI are documented elsewhere (see Johnston and Holzman36, Haimo and Holzman36, and Metsanen et al39). The TDI was chosen because it has proved to be an effective instrument for distinguishing manic from schizophrenic TD.8

Thought disorder was assessed in several ways, including total TDI score, number of responses, and number of thought-disordered responses. The total TDI score is calculated as the sum of the frequency of each instance of TD, multiplied by its severity weight, divided by the number of Rorschach responses to control for verbal productivity, and multiplied by 100 to express the value as a percentage:

$$TDI = \frac{0.25(A) + 0.50(B) + 0.75(C) + 1.00(D)}{\text{Total number of Rorschach responses}} \times 100,$$

where A = the number of responses scored at the 0.25 level, B = the number of responses scored at the 0.50 level, C = the number of responses scored at the 0.75 level, and D = the number of responses scored at the 1.00 level. Thus, higher scores on the total TDI indicate greater cognitive slippage.

We compared the groups in terms of 2 previously identified factors, namely, Idiosyncratic Verbalizations and Combinatory Thinking, which have been shown to distinguish schizophrenic TD from that of nonschizophrenic patients.6,12 The Idiosyncratic Verbalizations factor consisted of the Peculiar Verbalizations and the Queer Response categories (examples of peculiar verbalizations would be the following actual responses: It looks like ... “an ant’s eye view of a man” or “the ghost of a skeleton” [another subject’s response]). The Combinatory Thinking factor consisted of the following response categories: Congruous Combination, Idiosyncratic Symbolism, Fabulized Combination, Confabulation, Autistic Logic, and Contamination (examples of actual responses that contributed to the Combinatory Thinking factor score are: It looks like ... “a Koala bear with a green jacket and orange pants on” [Incongruous Combination] and “...two turkeys dancing on a butterfly” [Fabulized Combination]). Independent samples t-tests revealed that the 2 samples did not differ in terms of mean TDI score, number of responses, number of thought-disordered responses, number of odd (idiosyncratic) verbalizations, or number of combinatory thinking responses (t's ranged from 0.46 to 1.51, statistical nomenclature [n.s.]). Therefore, no major differences in TD emerged between Sample A and Sample B.

Assessment of Outcome Psychiatric Diagnoses

In examination rounds 4 through 7 of the NYHRP, the Schedule for Affective Disorders and Schizophrenia—Lifetime Version40 was administered to all participants aged 18 and older to assess Axis I disorders using the Research Diagnostic Criteria.41 Final diagnostic evaluations relevant to this report were conducted in 2002, at mean ages 39.62 ± 1.82 (Sample A) and 33.83 ± 2.06 (Sample B). Readers are referred elsewhere31,32 for detailed description of the diagnostic evaluations, which included all available clinical data: research interviews, psychiatric hospital records, and when relevant, therapists’ notes and comments.

Adulthood Axis I disorders were categorized according to the following hierarchy: (a) schizophrenia-related psychoses (including schizophrenia, unspecified functional psychosis, and schizoaffective disorder, mainly schizophrenia); (b) affective psychosis (psychotic major depression, bipolar I with psychosis, bipolar II with psychosis, manic psychosis, and schizoaffective disorder, mainly affective); (c) nonpsychotic affective disorders; (d) other major Axis I disorders (ie, anxiety disorders, substance abuse disorders); (e) drug-related psychosis; and (f) no disorder. Participants were also evaluated for the presence of schizotypal features using the Personality Disorder Examination (PDE42), a semistructured clinical interview designed to assess all Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) Axis II disorders. As described elsewhere,43 the diagnostic algorithm provided in the PDE was used. All interviews were administered by trained clinical psychologists or psychiatric social workers who were naïve to parental diagnostic group.

Statistical Analyses

For the remainder of the analyses, the 2 samples of the NYHRP were combined. We conducted a series of one-way ANOVAs (SPSS version 16.1) to perform the group comparisons with parental risk and adulthood outcome diagnosis as the independent variables. The main dependent variables were total TDI score, number of TDI responses, and the 2 a priori factors, namely, Idiosyncratic Verbalizations and Combinatory Thinking. Each ANOVA was followed by multiple comparisons using least significant differences tests.

The TDI data were nonnormally distributed. To normalize the skewness of the TDI variables and to increase the statistical power, we transformed the data to the natural logarithm of the raw score. All statistical analyses
were performed on the transformed scores. Group means for the TDI variables are reported here using the untransformed scores for ease of interpretation. In cases where there were disparate differences in group size, very small sample sizes, and/or considerable violations of assumptions of normal distribution and equality of variance, we used nonparametric statistical tests. Because of our directional a priori hypotheses regarding the relationship between schizotypal features and TD, one-tailed tests were applied.

Results
The subsample discussed in this report consisted of the 232 offspring who had been administered the Rorschach test in late adolescence/young adulthood: 63 (32 males, 31 females) individuals were genetically at-risk for schizophrenia (HRSz), 52 (20 males, 32 females) individuals were genetically at-risk for affective disorder (HRAff), and 117 (63 males, 54 females) were NCs. Overall, the mean age of the participants at the time of the Rorschach assessment was 19.6 years (range, 13–24 years).

Correlational analysis revealed significant associations among the TD variables. TDI scores were associated with number of thought-disordered responses, idiosyncratic verbalizations, and combinatory thinking in the combined sample of 232 offspring and in all 3 groups separately (r’s ranged from .51 to .83, P < .001). Similarly, the number of thought-disordered responses correlated with idiosyncratic verbalizations and combinatory thinking across the entire sample and in all 3 offspring groups separately (r’s ranged from .49 to .91, and .40 to .55, P < .001, respectively). Additionally, the HRAff group displayed a significant correlation (r = .41, P < .01) between their verbal productivity and TD, whereby the more responses they produced, the higher their idiosyncratic verbalization score.

Thought Disorder as a Function of Parental Diagnosis
Table 1 presents the descriptive statistics for the various TDI scores. Univariate ANOVA revealed significant group differences in the quantity of TD, as measured by the total TDI score, F(2,229) = 32.80, P < .001. HRSz offspring had significantly higher average TDI scores than either the HRAff offspring (P < .001; Glass’s effect size = 1.1 [Glass’s delta was used to calculate effect size because it takes into account unequal variances]. Cohen’s d assumes equal variances, which is not the case for the dependent measures[4]) or the NC offspring (P < .001; effect size = 2.1). The HRAff offspring also differed from the NC offspring (P < .05; effect size = 0.32).

The groups differed, too, in average number of Rorschach responses (F(2,229) = 4.29, P < .05). The HRSz offspring produced significantly fewer responses than the NC offspring. No other group comparisons reached significance. The results of the ANOVA showed that in addition to differing in their verbal productivity, the groups differed in their mean number of “thought-disordered” responses; follow-up analyses indicated that the HRSz group produced more thought-disordered responses than either the HRAff group (P < .001; effect size = 1.6) or NC offspring (P < .001; effect size = 2.15). The latter 2 groups did not differ from each other; effect size: 0.32. Thus, a greater proportion of the responses that the HRSz subjects produced were marked by TD than was the case for the other 2 groups. The disproportionate proportion of disordered responses produced by the HRSz group is also shown in table 2. A greater proportion of the HRSz subjects produced at least 1 response at the 0.75 level relative to the other 2 groups.

ANOVA with idiosyncratic verbalizations and combinatory thinking as the dependent variables and parental diagnosis as the independent variable demonstrated differences in the components of the groups’ TD responses. There was a significant group effect for idiosyncratic verbalizations, F(2,229) = 53.38, P < .001. Pairwise comparisons indicated that the HRSz group produced more odd verbalizations than either the HRAff (P < .001; effect size = 2.2) or the NC (P < .001; effect size = 3.2) groups, and the latter 2 groups did not differ from each other (effect size = 0.23). In contrast, the frequency of instances of combinatory thinking were rare in this subject population and did not vary as a function of parental diagnosis, F(2,229) = 0.01, n.s.

Thought Disorder in Offspring as a Function of Psychotic Outcome
We sought to investigate whether individuals with and without an adulthood diagnosis of psychotic disorder differed in TD at the earlier assessment, regardless of parental diagnosis. For this analysis, we excluded any individuals (n = 4) who had an outcome diagnosis of a drug-related psychosis. The resultant sample (n = 228) included offspring who at the follow-up evaluation met diagnostic criteria for either a schizophrenia spectrum psychotic disorder (n = 13) or an affective psychosis (n = 4). The parental group breakdown of these individuals with psychotic disorders is as follows: 71% (n = 12) were from the HRSz group, 18% (n = 3) from the HRAff group, and 12% (n = 2) from the NC group. Table 3 presents the TD data for the subjects classified according to outcome. We used the Mann–Whitney U test to compare the TD profiles of psychotic vs nonpsychotic individuals. The 17 offspring who developed a psychotic disorder in adulthood had significantly higher total TDI scores than those who remained free of psychosis, Z = 3.16, P < .01 (effect size = 0.94). Offspring who developed psychosis had a significantly higher combinatory thinking score (Z = 2.31, P < .05) than their nonpsychotic
counterparts; idiosyncratic verbalization factor scores were also higher, though this difference failed to reach statistical significance, \( Z = 1.70, P = .09 \). In both cases, the effect size was moderate (0.51–0.54).

We sought to further capitalize on this unique sample by comparing the presence of the a priori factors previously identified, namely, idiosyncratic verbalizations and combinatory thinking, in the offspring who later developed either schizophrenia-related or affective psychotic outcomes. Owing to the relatively low base rate of psychosis and the high variance of each factor score as well as the small number of individuals under study, we used Fisher’s Exact tests. The presence or absence of combinatory thinking was one dichotomous category, and the nature of the psychosis (ie, schizophrenia-related or affective) was the other dichotomous category. Over 60% (8/13) of the individuals with schizophrenia-related psychoses and none of those with affective psychoses (0/4) were rated as displaying evidence of combinatory thinking in their responses to the Rorschach (one-tailed Fisher’s Exact test, \( P = .05 \)). The relation between presence or absence of idiosyncratic verbalizations and the type of psychosis was not statistically significant.

The Association between Schizotypal Features and Formal Thought Disorder

Our second goal was to examine the association between schizotypal features and formal TD. Individuals with a diagnosis of psychosis and/or who may have been in the prodromal phase of psychosis were excluded from this analysis; interview-based schizotypal ratings were unavailable for 5 subjects from the NC group. Therefore, the analyses of schizotypal features and TD are based upon 206 of 232 individuals (89% of the sample).

Personality disorder symptom ratings on the PDE ranged from 0 to 8; a minimum rating of 5 was required for the individual to meet diagnostic criteria for schizotypal personality disorder. We computed a zero-order Pearson product-moment correlation coefficient between the PDE-derived ratings of schizotypal features and the TD measures. In the combined sample, the correlation between the schizotypal features ratings and TD variables were: TDI scores = 0.13 (\( P = .036 \)), number of thought-disordered responses = 0.12 (\( P = .039 \)), idiosyncratic verbalizations = 0.12 (\( P = .049 \)), and combinatory thinking = 0.03 (\( P = .358 \)) (all \( P \) values one-tailed). Thus, increased schizotypal features were associated with increased TD, both in general and with respect to the more specific categories of TD.

Discussion

The purpose of this investigation was to evaluate TD as a potential endophenotype and to examine the relationship of TD to clinical outcome in later adulthood. If TD

Table 1. Formal Thought Disorder Scores in Offspring by Parental Diagnosis

<table>
<thead>
<tr>
<th>Schizophrenia (HRSz)</th>
<th>Affective Disorder (HRAff)</th>
<th>No Mental Illness (NC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>Total Thought Disorder Index score</td>
<td>12.96 ± 16.8</td>
<td>4.93 ± 7.6</td>
</tr>
<tr>
<td>Number of Rorschach responses</td>
<td>6.08 ± 2.7</td>
<td>6.40 ± 2.0</td>
</tr>
<tr>
<td>Number of TD responses</td>
<td>2.59 ± 2.8</td>
<td>0.85 ± 1.1</td>
</tr>
<tr>
<td>Idiosyncratic Verbalizations</td>
<td>2.14 ± 2.5</td>
<td>0.38 ± 0.8</td>
</tr>
<tr>
<td>Combinatory Thinking</td>
<td>0.29 ± 0.7</td>
<td>0.27 ± 0.6</td>
</tr>
</tbody>
</table>

Note: Raw (untransformed) values are provided here for ease of interpretation. Significant between-group differences are noted; refer to text for details. *\( P < .05 \), **\( P < .01 \), ***\( P < .001 \), 2-tailed. NC, normal control.

Table 2. Percentage of Subjects with Highest TDI Rating at Each Level of Severity by Group

<table>
<thead>
<tr>
<th>TDI Category(^a)</th>
<th>HRSz, (n = 63)</th>
<th>HRAff, (n = 52)</th>
<th>NC, (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest rating at 0</td>
<td>23.8</td>
<td>48.1</td>
<td>67.5</td>
</tr>
<tr>
<td>Highest rating at 0.25</td>
<td>55.6</td>
<td>36.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Highest rating at 0.50</td>
<td>9.5</td>
<td>9.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Highest rating at 0.75</td>
<td>11.1</td>
<td>3.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Highest rating at 1.00</td>
<td>0.0</td>
<td>1.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Note: TDI, Thought Disorder Index. HRSz, offspring of the schizophrenia patients; HRAff, offspring of the affective disordered patients; NC, offspring of normal healthy controls.

\(^a\)TDI levels of severity are as follows: 0 indicates no TD; the TDI levels range from 0.25 (very mild) to 1.0 (reflecting the most severe). Readers are referred to Johnston and Holzman\(^{36}\) and Solovay et al\(^{37}\) for details.
Thought Disorder in High-Risk Offspring

Table 3. Formal Thought Disorder Scores in Offspring Classified by Presence of Later Psychosis

<table>
<thead>
<tr>
<th></th>
<th>Psychosis, ( n = 17 )</th>
<th>No Psychosis, ( n = 211 )</th>
<th>( Z )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought Disorder Index score</td>
<td>14.66 ± 16.3</td>
<td>5.05 ± 10.2</td>
<td>3.16</td>
<td>**</td>
</tr>
<tr>
<td>Number of Rorschach responses</td>
<td>5.94 ± 2.4</td>
<td>6.91 ± 3.2</td>
<td>1.28</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of TD responses</td>
<td>2.59 ± 2.6</td>
<td>1.05 ± 1.8</td>
<td>3.00</td>
<td>**</td>
</tr>
<tr>
<td>Idiosyncratic Verbalizations</td>
<td>1.59 ± 2.3</td>
<td>0.72 ± 1.6</td>
<td>1.70</td>
<td>n.s.</td>
</tr>
<tr>
<td>Combinatory Thinking</td>
<td>0.56 ± 0.8</td>
<td>0.25 ± 0.6</td>
<td>2.31</td>
<td>*</td>
</tr>
</tbody>
</table>

*Note: Raw (untransformed) values are provided here for ease of interpretation. This analysis does not include subjects with drug-induced psychosis. Results of Mann–Whitney U test nonparametric test for equality of means are presented here. \( *P < .05 \), \( **P < .01 \), 2-tailed.*

were an endophenotype, then it would be expected to be present in individuals at heightened genetic risk for schizophrenia, regardless of whether they (subsequently) are affected by the disorder. Thus, in this study, the HRSz group should display more TD than the NC group. Analyses based upon the NYHRP sample extend the extant literature in 2 ways: (1) by including individuals at heightened genetic risk for nonschizophrenic disorders who would be expected to show less TD than HRSz subjects and (2) by consideration of both global and specific indices of TD.

As expected, the HRSz offspring did produce more TD, as reflected by significantly higher TDI scores, than either the HRAff offspring or the NC offspring. The HRSz offspring showed lower verbal productivity than did subjects in the other 2 offspring groups, meaning that TD was reflected in a greater proportion of their verbalizations. This is interesting because low verbal productivity suggests poverty of speech, one of the negative symptoms of schizophrenia. These findings confirm earlier reports suggesting that the high-risk offspring of schizophrenic parents display more TD than offspring of controls or offspring of affectively disordered parents. Results from the present report complement earlier findings based upon a subset of the NYHRP children at a mean age of 9.5 years old. Ott et al, who looked at videotaped clinical interviews and scored TD according to the Scale of Thought, Language, and Communication, observed elevated TD in individuals who developed schizophrenia-related psychoses. (Data from the present analysis and that of Ott et al cannot be compared. The subsets of NYHRP children examined for TD in this report and that of the earlier one overlap somewhat but are not identical. Subjects were not selected intentionally; they represent all the offspring who received the measures relevant to the given analysis.)

In addition to finding quantitative differences in formal TD as a function of parental diagnosis, we observed differences in type of disordered thinking. The HRSz group produced significantly more idiosyncratic verbalizations (ie, instances of peculiar word usage) than either the HRAff group or the NC group. This finding is consistent with prior reports indicating that the TD of relatives of schizophrenia probands is characterized primarily by idiosyncratic verbalizations. The results are also consistent with the observation that high-risk adoptees displayed greater instances of peculiar word usage than control adoptees. Taken together, our results indicate that individuals at heightened genetic risk for schizophrenia display greater TD, whether assessed by global or more specific indices, than individuals at low genetic risk for schizophrenia. These findings are consistent with TD as an indicator of a schizophrenia diathesis, one that becomes worse with illness onset.

We also found evidence of increased amounts of TD in those adolescents/young adults with later psychosis. However, this effect was driven largely by the HRSz group, which accounted for the majority of cases of adult psychosis. Offspring who developed psychosis not only received higher TDI scores but also demonstrated more instances of combinatory thinking than nonpsychotic offspring. Nonetheless, given prior research indicating that schizophrenia patients display few instances of combinatory thinking, whereas manic patients display many, it is unlikely that combinatory thinking can serve as an endophenotypic marker of a genetic diathesis for schizophrenia.

There was evidence that TD may be a pleiotropic manifestation of a trait that co-occurs with other expressions of schizotypy, such as schizophrenia or schizotypal features. Various aspects of formal TD, as measured by the TDI, and schizotypal features, as measured by the PDE, were positively correlated. The greater the amount of TD at an average age of 19 years, the more likely that person was to exhibit schizotypal features in their mid- to late thirties. The modest but significant relationship between TD during late adolescence and adult schizotypal features is consistent with reports of TD in psychometrically identified schizotypes and in schizotypal personality disordered patients. One alternative account for the observed relationship between TD and schizotypal features is that TD in late adolescence constitutes an initial sign of psychosis and/or schizotypy.
important to note, however, that TD may be both a *forme fruste* of the disorder in someone who later becomes ill as well as a possible pleiotropic effect of a risk gene in both penetrant and nonpenetrant gene carriers.

Limitations of the study include the fact that the sample is entirely comprised of Caucasian participants. A sample that is more representative of the general population would be desirable to enhance the generalizability of these results. Furthermore, since the NYHRP sample consisted of clinically unaffected relatives, the TD that was detected was more subtle and considerably less frequent than the TD that would accompany a psychotic illness. Thus, it would have been optimal to have had a larger sample of responses from which to assess TD, ie, responses to 10 Rorschach cards rather than 4.

Despite these limitations, the data show unequivocally that the offspring of schizophrenia patients exhibit significantly more TD than the offspring of affective disordered parents and psychiatrically healthy parents. Because longitudinal studies of clinical outcome in high-risk samples are scarce, there are comparatively few data addressing whether premorbid TD is more generally associated with genetic risk, independent of the later development of psychosis. Additional strengths of this study include the fact that raters of TD were naïve to the offspring’s (parental diagnosis) group status as well as the fact that the diagnostic evaluations encompass the maximum period of risk for manifestation of schizophrenia.

These data, considered along with the extant corpus of literature based largely upon the TDI, support the notion that aspects of TD may serve as phenotypic indicators of a genetic liability for schizophrenia. It is possible that global TD may serve both as an indicator of a clinical state (eg, prodrome, psychosis, and remission) and as an independent, alternative expression of a genetic diathesis (eg, prodrome, psychosis, and remission) that is a pleiotropic characteristic. Our findings are consistent with both of these possibilities. The observation that the offspring of schizophrenic parents displayed a greater likelihood of idiosyncratic verbalizations suggests that specific types of TD may serve as phenotypic indicators of a schizophrenia diathesis.

Endophenotypes offer a valuable means of improving the identification of nonpenetrant gene carriers. Using behavioral endophenotypes, instead of, or in addition to the presence of a clinical disorder, to help case identification can assist investigators in the detection of genes conferring risk for schizophrenia. As such, the presence of TD in a schizophrenic proband’s relatives may enrich the power of genetic studies of this illness.

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**References**


Thought Disorder in High-Risk Offspring


