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Thought Disorder in Schizophrenia and Bipolar Disorder Probands, Their Relatives, and Nonpsychiatric Controls

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Thought disorder (TD) has long been associated with schizophrenia (SZ) and is now widely recognized as a symptom of mania and other psychotic disorders as well. Previous studies have suggested that the TD found in the clinically unaffected relatives of SZ, schizoaffective and bipolar probands is qualitatively similar to that found in the probands themselves. Here, we examine which quantitative measures of TD optimize the distinction between patients with diagnoses of SZ and bipolar disorder with psychotic features (BP) from nonpsychiatric controls (NC) and from each other. In addition, we investigate whether these same TD measures also distinguish their respective clinically unaffected relatives (RelSZ, RelBP) from controls as well as from each other. We find that deviant verbalizations are significantly associated with SZ and are co-familial in clinically unaffected RelSZ, but are dissociated from, and are not co-familial for, BP disorder. In contrast, combinatory thinking was nonspecifically associated with psychosis, but did not aggregate in either group of relatives. These results provide further support for the usefulness of TD for identifying potential non-penetrant carriers of SZ-risk genes, in turn enhancing the power of genetic analyses. These findings also suggest that further refinement of the TD phenotype may be needed in order to be suitable for use in genetic studies of bipolar disorder.

Key words: schizophrenia/bipolar disorder/heterogeneity/thought disorder/endophenotype/genetics

Introduction

Cognitive dysfunction is a fundamental component of serious mental illness (SMI),[1–10] has a major impact on functional disability and psychosocial outcome[8,11–19] and is a risk factor for conversion to psychosis in high-risk samples.[20–27] One key feature of cognitive dysfunction is thought disorder (TD). TD has been regarded as a hallmark of schizophrenia (SZ) since Kraepelin[28] and Bleuler[29,30] first described the disordered thought processes of SZ patients as "derailments" and "loosening of associations," respectively. Subsequent investigations confirmed the presence of disordered thinking not only in SZ, but also in affective and other psychotic conditions and in some organic brain diseases.[31–43]

There is now agreement that TD is a transdiagnostic symptom, even though different clinical disorders have distinct TD profiles and some features of TD are nonspecific.[38–42,44–46] Andreasen and colleagues, eg, found that poverty of speech and content were more characteristic of SZ than of mania. Pressured speech, clanging, distractible speech, and circumstantiality were more strongly associated with mania. The 2 groups did not differ in the frequency of other indicators of TD (derailment, tangentiality, illogicality, incoherence, and loss of goal).[38] Using the Thought Disorder Index (TDI), Holzman and colleagues reported that extravagantly (and often playfully) combined ideas (combinatory thinking) and irrelevant intrusions characterized mania, whereas disorganization and frequent idiosyncratic word usage characterized SZ.[41,42,45] The TD of schizoaffective patients tended to resemble primarily that seen in SZ.[39,41,45,46] The fact that TD transcends formal diagnostic categories is consistent with the nonspecificity of many symptoms of SMI and with the nonspecificity of many cognitive and biological phenotypes in probands and in their clinically unaffected relatives.[6,47–60] This nonspecificity is also consistent with the substantial (but incomplete[61,62]) overlap in genetic susceptibility loci across psychiatric disorders[63–70] and with recent work

documenting that the familial aggregation of psychiatric disorders is much less specific than had been thought.[71–77]

Both Kraepelin and Bleuler observed that the biological family members of SZ patients often displayed what appeared to be attenuated SZ traits (eg, odd speech), and concluded that the psychopathology of SZ was not limited to the psychotic form of the illness. Bleuler referred to such states as latent SZ, which he considered to be a "diluted" form of the illness that included the central feature of "loosening of associations." He also observed that latent SZ was more prevalent among the biological relatives of SZ patients than was manifest psychosis. In the formulations of the "schizotype" by Rado[78] and Meehl,[79,80] mild TD, or "cognitive slippage," was considered a core feature. Meehl considered cognitive slippage to be a reflection of a genetic liability for SZ; in his view, most individuals with the hypothetical schizotaxic predisposition remained nonpsychotic and non-schizoptypic.[79]

An extensive body of empirical research, using a variety of measures to assess TD, has confirmed the presence of mild TD or odd speech in clinically unaffected relatives of SZ patients[42,44,81–98] and in high-risk offspring.[20,99–106] Notably, the biological relatives of SZ (RelSZ) adoptees have significantly higher TD scores than adoptive RelSZ.[92] Similarly, idiosyncratic verbalizations are significantly more prevalent in adopted biological offspring of SZ mothers than in adopted offspring of control mothers.[107] Also, the biological parents of SZ individuals have significantly more deviant associations than do their adoptive parents.[108] The results of these adoption studies strongly support the conclusion that genetic factors are involved in the multiple independent replications of the familial aggregation of thought, language and communication disorders in SZ families, although an interaction between genetic vulnerability and psychosocial risk factors, such as parental communication deviance, may also play a role.[109,110] Of particular importance, the TD found in clinically unaffected biological RelSZ tends to be qualitatively similar to (but milder than) that found in the probands.

Like TD, communication and language deviance show a significant propensity to aggregate among biological RelSZ.[82–84,95,103,111–116] The strong association of thought, language and communication disorders with SZ and their over-representation in clinically unaffected first-degree relatives suggest that one or more aspects of these behaviors may productively inform genetic studies. Idiosyncratic verbalizations, which involve unusual semantic formulations, are a core characteristic of TD, anomalous use of language, and communication disturbances. Semantic anomalies, in particular, seem to be a consistently identified linguistic component of the disease and possibly of genetic liability for it. Indeed, idiosyncratic word usage is a component of most scales used to assess TD,[44,117–119] language and thought,[120,121] and language and speech[122] (reviewed in detail in ref.[123]). Importantly, the findings in clinically unaffected individuals provide evidence that most TD scales are sensitive even to the mild TD that can be present in the absence of psychosis.

Despite the recognition that TD is a component of affective disorders, mania in particular, it has not been as extensively studied in these patients as in SZ patients and even less so in their biological relatives.[98]

In the current study we extend previous work based on the TDI in order to characterize the quantitative features of TD in substantially larger samples of patients and relatives. The 2 goals are: (1) to identify the quantitative measures of TD that optimize the distinction between probands with diagnoses of SZ and bipolar disorder with psychotic features (BP) and between each proband group and controls, and (2) to determine whether the same quantitative TD features optimize the distinction between their respective relatives groups and distinguish each group of relatives from controls. The results bear on the usefulness of different TD profiles as endophenotypes for SZ and BP disorder, and on the potential utility of TD as a transdiagnostic endophenotype.

Methods

Participants

The subject groups included patients with a diagnosis of SZ (n = 102), schizoaffective disorder (SA; n = 141), and bipolar I disorder with psychotic features (BP; n = 79; most recent episode manic, n = 50; most recent episode depressed, n = 12; most recent episode mixed, n = 17); nonpsychiatric control (NC) subjects (n = 184); and clinically unaffected first-degree biological relatives of the patient groups: relatives of SZ patients (RelSZ; n = 121), relatives of schizoaffective patients (RelSA; n = 151), and relatives of bipolar disorder patients (RelBP; n = 40). All probands were assessed as outpatients and were recruited approximately 6 months after discharge from McLean Hospital. All relatives were relatives of these probands. Demographic characteristics of the sample are presented in table 1. These subjects were recruited over a 15-year period. Relatives were considered clinically unaffected if they did not meet *DSM-IV* criteria for any psychotic disorder (lifetime), bipolar disorder without psychotic features, or a SZ-spectrum personality disorder. The NC group was restricted to individuals who met the criteria for being clinically unaffected in relatives of probands but also had no family history of psychosis, suicide, or psychiatric hospitalizations.

Axis I disorders were assessed in all subject groups using the Structured Clinical Interview for *DSM-IV*, Patient Edition.[124] Schizotypal, schizoid, and paranoid personality disorders were assessed in the NC subjects and the relatives groups using a modified version of the Structured Interview for Schizotypal Symptoms.[125] An experienced clinician administered the interviews, and an independent group of senior diagnosticians reviewed the interview material and all available hospital records and assigned consensus Axis I and Axis II diagnoses based on best estimate

Table 1. Demographic Characteristics (Mean/SD) of the Study Sample

Group	*N*	Age	Gender (% Male)	Years of Education	Duration of Illness[a]	BPRS[b]	GAS[c]
Schizophrenia (SZ) patients	242	38.7 (9.5)	55.0%[d]	14.0 (2.3)[e]	15.6 (9.7)[f]	48.0 (14.7)[g]	37.4 (9.8)[h]
Bipolar patients	79	35.8 (10.4)	36.7%	15.4 (2.4)	11.2 (9.5)	34.3 (9.2)	51.1 (11.7)
Normal control subjects	184	39.1 (15.0)	40.8%	15.0 (2.4)	—	—	—
Relatives of SZ patients	272	51.3 (16.7)[i]	34.2%	15.3 (2.6)	—	—	—
Relatives of bipolar patients	40	42.0 (12.1)	22.5%	15.6 (2.5)	—	—	—

Note: RelSZ, relatives of schizophrenia patients; RelBP, relatives of bipolar disorder patients; GAS, Global Assessment Scale; BPRS, Brief Psychiatric Rating Scale.
[a]Duration of illness is defined as number of years since first hospitalization.
[b]BPRS was missing for 4 SZ and 1 BP.
[c]GAS was missing for 1 SZ and 1 BP.
[d]SZ patients were disproportionately male compared with normal controls ($P = .040$), RelSZ ($P < .001$), and RelBP ($P = .003$); the difference between the proportion of men in the SZ and BP groups did not reach statistical significance ($P = .05$).
[e]SZ patients had significantly fewer years of education compared to all other groups ($P < .001$ for each pairwise comparison).
[f]SZ patients had significantly longer duration of illness compared to BP ($P = .001$).
[g]SZ patients had significantly higher BPRS than BP ($P < .001$).
[h]SZ patients had significantly lower GAS than BP ($P < .001$).
[i]RelSZ were significantly older than all other groups ($P < .001$ for each pairwise comparison using the Tukey-Kramer test).

methods[126] using *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) criteria.[127] Agreement between pairs of diagnosticians is excellent (0.84–1.00) for individual Axis I and Axis II diagnoses, and for no diagnosis. The interviewers and diagnosticians were both blinded to group membership and the results of the TD procedures. The following exclusion criteria applied to all participants: (1) lack of fluency in English; (2) history of serious head trauma or diagnosed organic brain disease; (3) history of substance abuse or dependence during the past 2 years or previous chronic dependence. All participants provided written informed consent.

Procedure

All subjects were administered a 10-card Rorschach Test[128] following the procedures described in Rapaport, Gill, and Shafer.[129] All sessions were audiotaped and subsequently transcribed verbatim. The protocols were scored for TD according to the revised TDI scoring manual[119] by a consensus team of expert raters who were blinded to group membership. Both the Rorschach administration and TDI scoring were performed independently of the diagnostic interviewers and by different individuals.

The TDI distinguishes 23 categories of TD that are weighted along a continuum of severity (.25, .50, .75, and 1.0), with the .25 level representing very mild forms and the 1.0 level reflecting the most severe forms of TD. The total TDI score has high inter-rater reliability[130] and is unrelated to race, gender, socioeconomic status, or IQ.[44,131] Detailed descriptions and examples of the individual TD scoring categories are provided elsewhere.[44,119,123,132]

Quantitative TD Phenotypes. The total TDI score was calculated as previously described.[119] The total TDI score reflects the total amount of TD, but does not identify the nature of the TD that is present. That is, the same total score may be comprised of very different TD dimensions. Two dimensions that were identified in previous studies to distinguish between patient and relatives groups are deviant verbalizations (DVs) and combinatory thinking (CT).[41,42,45,98] For each subject we calculated a DV score and a CT score, each of which was based on the sum of instances of TD in each of these categories (eg, peculiar, queer, absurd responses for DVs; incongruous and fabulized combinations, playful and other confabulations for CT).

Examples of SZ-related DVs include: "rectangularly speaking"; "the mineral of its substance"; "an x axis in origin"; "posterior pronunciations"; "the outform of the map"; and "a nonverbal misrepresentation leading to an unformulated thought." DVs are readily identifiable in settings independent of the formal assessment of TD, as in these chief complaints: "I'd like to discontinue zyprexa and SZ tool bar disorder;" "I am an aspect recruit of biophysics." Stilted or awkward word usage can occur in nonpsychiatrically ill individuals but usually lacks the malignant quality of the idiosyncratic word usage seen in SZ-related DVs.

CT involves finding relationships between unrelated things, but these vary qualitatively in different contexts. Mild, infrequent instances of CT are not pathological, but more severe forms generally accompany psychotic conditions. In CT, in the context of mania, loosely linked ideas are extravagantly combined and elaborated, as is also seen clinically in the grandiosity and expansiveness of mania. Manic CT is often playful and humorous, even in the context of outlandish embellishments. Some examples of mania-related CT from the TDI include: "parasitic orchids living on puddles of blood;" "babies playing

the saxophone and peeing daffodils"; "two women who just had babies are thinking about how much they love their babies, which is why their thoughts are shaped like fetuses and their hearts are popping out of their bodies." Counterparts exist for psychotic depression and nonaffective psychosis, including SZ and delusional disorder, each of which has distinctively recognizable qualities. Thus, more severe manifestations of CT are a component of all SMI, but are manifested differently in different clinical conditions.

Statistical Analyses

The dependent measures were the total number of DV responses, the total number of CT responses, and the total TDI score. The Kruskal-Wallis and Fisher's Exact tests were used to compare patient groups on the DV and CT scores. For any significant overall group differences, post hoc pairwise comparisons were conducted; in order to account for multiple comparisons, we used corrected Wilcoxon rank sum tests (for continuous outcomes)[133–135] and Bonferroni-corrected Fisher's exact tests (for categorical outcomes). In order to account for the nonindependence of observations in relatives of patients and among NCs, we also used generalized linear mixed models to compare groups. The concordance index, or area under the ROC curve, was used as a measure of discriminative power.

Following previous research,[136] we applied a novel hierarchical finite mixture model that accommodates correlated (ie, nonindependent) observations to model the DV and CT scores. Hierarchical modeling is appropriate because subjects were drawn from 314 families (151 NC families, 29 BP families, and 134 SZ families). Mixture modeling approaches are especially useful for analyzing traits that are heterogeneously distributed in a group. Endophenotypes are a good example, in that some relatives perform abnormally on an endophenotype measure and others perform normally, which may be related to the fact that a sample of unaffected relatives is likely a mixture of (non-penetrant) gene carriers and non-gene carriers.

The model used has been discussed in detail elsewhere[136]; a condensed description is provided here (see also supplementary material for further details). For each of DV and CT, we fit a series of finite mixture models:

Model 1: One hierarchical, zero-inflated Poisson (ZIP)[137] was fit to the data with the assumption of no mixture.

Model 2: A 2-component mixture of 1 ZIP and 1 Poisson was fit to the data with the assumption that the same mixing proportion was applicable for all 3 groups.

The Poisson distributed component is assumed to have a larger mean score than the ZIP component and corresponds to the high-risk group. Assuming the mixing proportion (ie, the probability of belonging to the high-risk class) does not differ by group implies that RelSZ and RelBP are at no higher risk for TD as measured by DV or CT than normal controls.

Model 3: A 2-component mixture of 1 ZIP and 1 Poisson was fit to the data. Different mixing proportions were assumed for each of the 3 groups.

As with model 2, the Poisson component corresponds to the high-risk class. Permitting the mixing proportion to vary by subject group allows a test of whether RelSZ or RelBP have significantly greater risk of TD than NC.

All analyses were conducted using SAS version 9.4 (SAS Institute). For all analyses, $P < .05$ was considered statistically significant.

Results

Neither the DV or CT score nor the Total TDI score differed between SZ and SA patients, or between the respective unaffected relatives of these patient groups (all P values > .05). Thus, in the analyses these groups were combined into a SZ patient group, and an unaffected relatives of SZ patients (RelSZ) group. Table 2 presents the means and standard deviations of the quantitative TD phenotypes in the subject groups.

Total TDI scores differed significantly among the 5 subject groups ($P < .001$).The SZ group had significantly higher Total TDI scores than NC and BP patients ($P < .001$, for both), with estimated effect sizes (ES) of 0.90 and 0.61, respectively. Similarly, the RelSZ had significantly higher total TDI scores than the NC ($P = .016$) and RelBP ($P = .027$), with estimated ES of 0.23 and 0.44, respectively. Bipolar patients also had significantly higher total TDI scores than NC ($P = .003$; ES = 0.44), but their relatives did not significantly differ from NC ($P > .2$). Results for all pairwise comparisons can be found in the supplementary material.

We also examined whether the subject groups differed in relation to the proportion of individuals who showed any TD (ie, a total TDI score >0). A significantly larger proportion of SZ showed TD than BP ($P = .033$), NC ($P < .001$), RelBP ($P < .001$) and RelSZ ($P = .003$). A significantly larger proportion of RelSZ also showed TD than NC ($P = .010$) and RelBP ($P = .033$; table 2).

In addition, we examined the distribution of TD severity in the 5 subject groups (table 2). The vast majority of instances of TD is in the mild to moderate range. Severe instances of TD occur intermittently, usually in the presence of mild-moderate instances of TD, and are typically found in psychotic individuals. Subjects were classified as having severe TD if they had at least one instance of TD at the 0.75 or 1.0 level (regardless of whether they also had instances of mild-moderate severity TD). Subjects were classified as having mild-moderate TD if all instances of TD were at the 0.25 or 0.50 severity levels only. Among

Table 2. Thought Disorder Measures (Mean/SD) and Severity (*n*, %) by Subject Group

	Subject Groups				
	Schizophrenia (SZ) Patients (*N* = 242)	Bipolar Patients (*N* = 79)	Normal Control Subjects (*N* = 184)	Relatives of SZ Patients (*N* = 272)	Relatives of Bipolar Patients (*N* = 40)
Deviant verbalizations	5.8 (5.6)	1.9 (3.3)	1.9 (3.4)	3.4 (4.5)	1.2 (1.7)
Combinatory thinking	3.5 (3.0)	2.7 (2.3)	1.6 (2.2)	1.5 (2.3)	1.2 (2.1)
Total TDI score	23.2 (23.3)	10.5 (10.4)	6.5 (8.4)	8.7 (10.4)	4.3 (5.2)
TD severity					
None	16 (6.6%)	14 (17.7%)	56 (30.4%)	47 (17.3%)	15 (37.5%)
Mild to moderate	72 (29.8%)	36 (45.6%)	87 (47.3%)	162 (59.6%)	19 (47.5%)
Severe	154 (63.6%)	29 (36.7%)	41 (22.3%)	63 (23.2%)	6 (15.0%)

Note: TD, thought disorder; TDI, Thought Disorder Index.

subjects with TD, SZ had a higher proportion of severe TD than BP ($P = .006$), NC ($P < .001$), RelBP ($P < .001$) and RelSZ ($P < .001$). The other groups did not significantly differ from one another in the rate of severe TD.

DV scores significantly differed among the 5 subject groups ($P < .001$). Histograms of the DV scores by subject group are displayed in figures 1A–E, and show that the distributions of DV scores for SZ and RelSZ are distinct from those of the other groups. SZ patients produced significantly more DVs than BP patients and NC subjects ($P < .001$, for both). Similarly, the RelSZ had significantly more DVs than NC subjects ($P < .001$) and RelBP patients ($P = .012$). The estimated ES for the comparisons of SZ and RelSZ with NC were 0.82 and 0.38, respectively (figure 1F). DVs had a concordance index of 0.76 for distinguishing between SZ and NC and a concordance index of 0.62 for distinguishing between RelSZ and NC, indicating good discrimination.[138] Neither BP patients nor RelBP differed from NC in DVs ($P > .20$, for both), corresponding to estimated ES of 0.01 and −0.22, respectively.

One hundred fifty-five (57.0%) of the clinically unaffected RelSZ had nonpsychotic Axis I disorders (eg, major depressive, anxiety disorders). DV scores for this subgroup did not significantly differ from the 117 (43.0%) RelSZ who did not meet criteria for any Axis I disorder ($P > .1$). This result suggests that non-SZ-related Axis I disorders do not account for the increased DV scores in clinically unaffected RelSZ.

CT scores also significantly differed among the 5 subject groups ($P < .001$). Both SZ and BP patients produced significantly more instances of CT than NC subjects ($P < .001$, for both) with ES of 0.74 and 0.50, respectively; SZ and BP subjects did not differ from each other ($P > .2$). CT had estimated concordance indexes of 0.72 and 0.66 for distinguishing between SZ and NC and between BP and NC, respectively, indicating good discrimination. The 59 BP patients who met criteria for a current BPD with psychotic features and the 20 BP who were in either full or partial remission did not differ in CT score or total TDI score ($P > .20$, for both), indicating that elevated CT and total TDI scores in BP are not dependent on current psychotic state. Furthermore, neither CT score nor total TDI score significantly differed by subtype of most recent BP episode ($P > .2$). Neither RelSZ nor RelBP differed from NC in CT ($P > .20$, for both), corresponding to estimated ES of −0.03 and −0.19, respectively.

In order to get a preliminary idea if further refinement of the CT phenotype would optimize the discrimination of patient and relatives' groups from controls, we blindly classified instances of CT as "BP" or "non-BP" in a random subset of subjects (24 SZ, 37 BP, 46 RelSZ, 40 RelBP, and 69 NC) and summed the scores for this subtype.

Both BP probands ($P < .001$) and RelBP ($P = .019$) showed significantly more "BP" CT than NC, with concordance indexes of 0.64 and 0.58, respectively, consistent with poor discrimination that may be a function of the relatively small sample sizes. Notably, the estimated ES for the comparisons of BP and RelBP with NC were substantially larger with the more narrowly defined CT score: 0.88 and 0.51, respectively. Neither SZ nor RelSZ differed from NC in "BP" CT ($P > .2$, for both; see supplementary figure 1).

Mixture Models

Random effects were included in each model to accommodate nonindependence of family members. As can be seen in figures 1 and 2, there is a relatively large proportion of zero-valued observations in all subject groups (ie, DV or CT scores of zero) suggesting that zero-inflated distributions are also needed to appropriately model these data. Due to a previous finding that DVs were more common in male subjects,[136] sex effects were included in each model. The Akaike information criterion (AIC) was used to compare models[139]; a lower value of AIC indicates a better fitting model.

For DV, model 3 (AIC = 2048.8) provided a better fit to the data than either model 1 (AIC = 2415.3) or model 2 (AIC = 2065.4), indicating that the 2-component mixture with different mixing proportions for each group

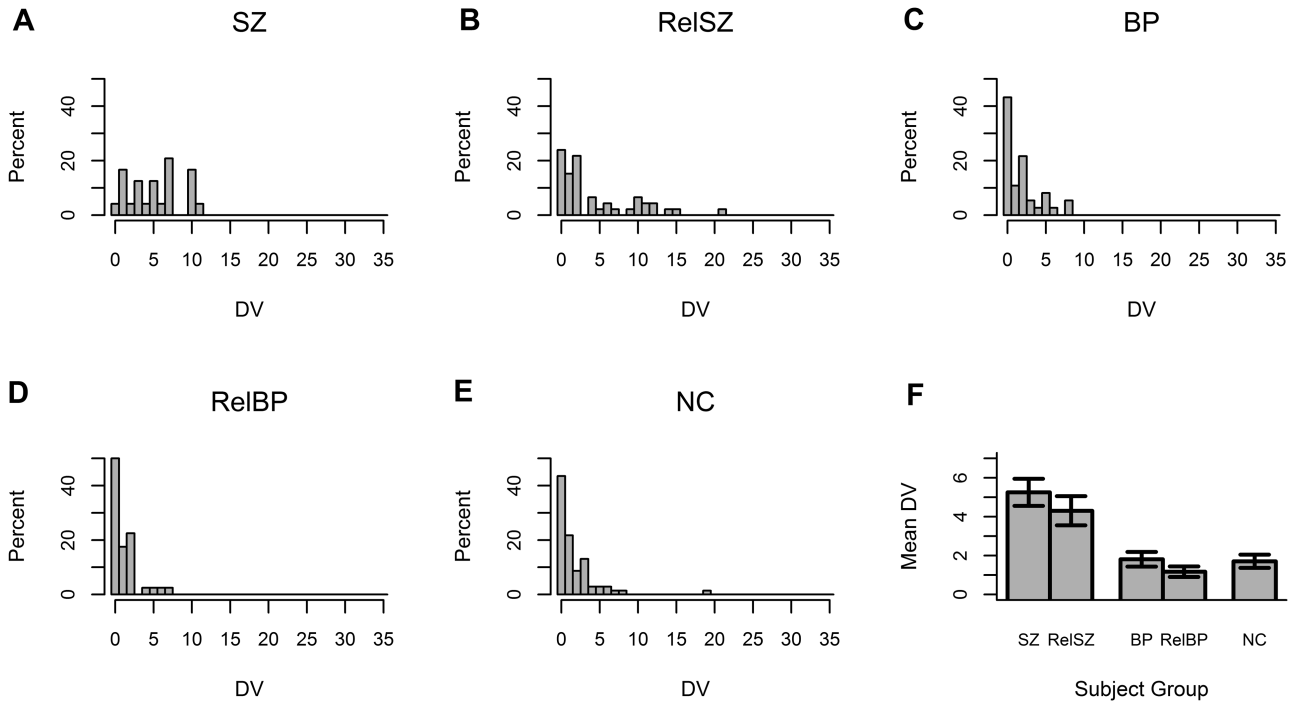

Fig. 1. Distributions of DVs in (A), RelSZ (B), BP (C), RelBP (D), and NC (E). Average DV for each group with SE bars are shown in 1F. *Note*: DVs, deviant verbalizations; BP, bipolar disorder with psychotic features; RelSZ, relatives of schizophrenia patients; NC, nonpsychiatric control; RelBP, relatives of bipolar disorder patients.

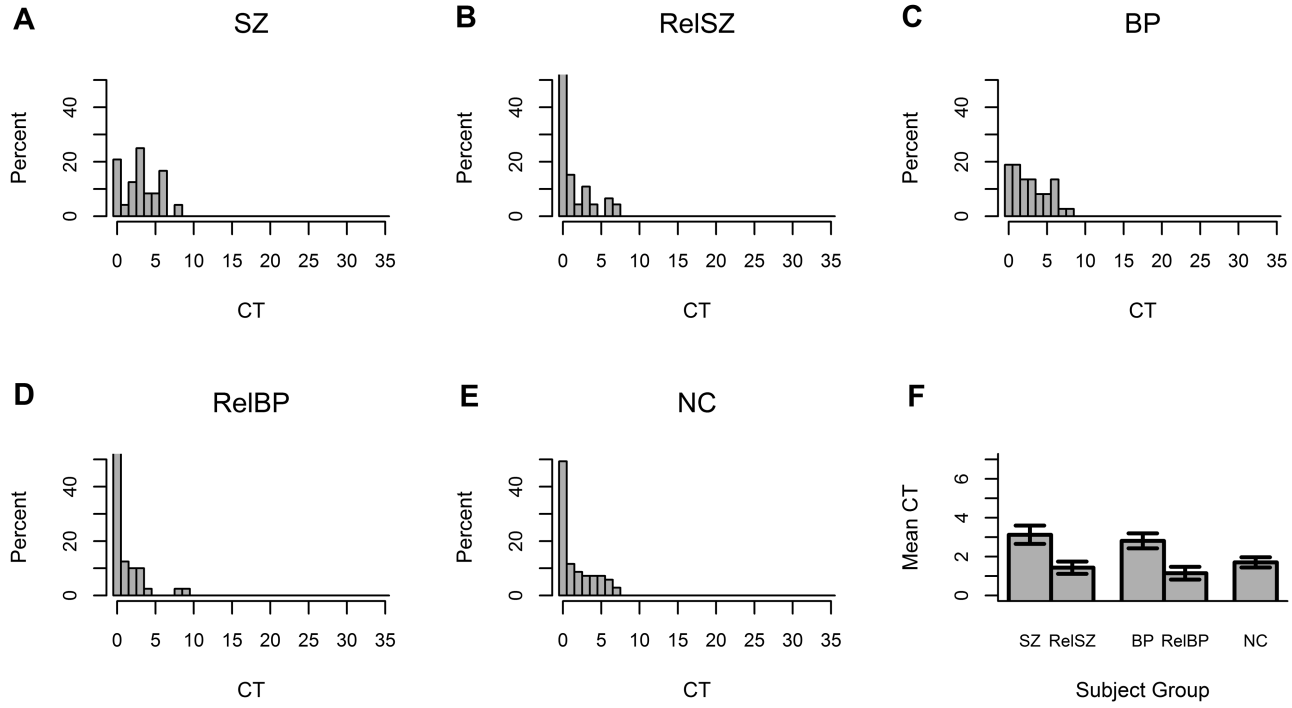

Fig. 2. Distributions of CTs in (A), RelSZ (B), BP (C), RelBP (D), and NC (E). Average DV for each group with SE bars are shown in 2F. *Note*: CT, combinatory thinking; DV, deviant verbalizations; BP, bipolar disorder with psychotic features; RelSZ, relatives of schizophrenia patients; NC, nonpsychiatric control; RelBP, relatives of bipolar disorder patients.

best described the distribution of DV scores. Results for this model (table 3) show that RelSZ are significantly more likely to be at high risk for DV than both NC ($P < .001$) and RelBP ($P = .034$). The mixing proportions for RelBP and NC did not differ ($P > .2$). For a RelSZ, the probability of belonging to the high-risk class is an

Table 3. Mixture Model Results

DV	High-risk Class	Low-risk Class
Poisson mean		
Male	11.0 (9.6, 12.7)	1.9 (1.5, 2.3)
Female	8.4 (7.1, 10.0)	1.4 (1.1, 1.8)
Rate of zero-inflation	—	33.1% (25.9%, 41.2%)
Probability of belonging to high-risk class		
NC	10.0% (6.0%, 16.3%)	
RelBP	4.3% (0.7%, 22.8%)	
RelSZ	25.5 (19.5%, 32.7%)	
CT	High-risk class	Low-risk class
Poisson mean	4.7 (3.7, 6.0)	1.2 (0.7, 2.0)
Rate of zero-inflation	—	44.7% (34.7%, 44.9%)
Probability of belonging to high-risk class		
NC	20.3% (11.3%, 33.5%)	
RelBP	(same as NC)	
RelSZ	(same as NC)	

Note: DV, deviant verbalizations; CT, combinatory thinking; RelSZ, relatives of schizophrenia patients; NC, nonpsychiatric control; RelBP, relatives of bipolar disorder patients.

estimated 25.5%; for NC and RelBP, the probabilities are 10.0% and 4.3%, respectively. These results indicate that there is significant heterogeneity in DV scores and that the distribution of DV is significantly different in RelSZ compared with NC or RelBP. In this larger sample, male subjects continued to have significantly higher DV scores than female subjects ($P = .004$).

For CT, model 2 (AIC = 1640.8) fit the data better than both model 1 (AIC = 1702.3) and model 3 (AIC = 1642.2; table 3). Thus, all subject groups shared the same probability of being at high risk for high CT scores. That is, a 2-component mixture with common mixing proportions provided the best fit, suggesting that there is significant heterogeneity in CT scores, but this heterogeneity is not tied to subject group. An estimated 20.3% of subjects belong to the high-risk class. There was no significant sex effect for CT scores ($P > .2$).

Discussion

Our data indicate that a quantitative TD phenotype, DVs, is significantly associated with SZ and is co-familial in clinically unaffected RelSZ, but is *dissociated* from, and is *not co-familial* for, BP disorder. RelSZ had a significantly higher probability of having a high DV score than RelBP or NC, supporting the usefulness of this measure in identifying a subgroup of RelSZ who do not have SZ-related clinical conditions yet have elevated amounts of SZ-related TD. Importantly, increased DV in RelSZ are independent of the presence of non-SZ-related nonpsychotic Axis I disorders. In contrast, CT was nonspecifically associated with psychosis among probands and did not aggregate in either group of relatives. As expected, the Total TDI score also was nonspecifically associated with psychosis. Although RelSZ had significant increases in this score, the ES were substantially smaller than for DV. These findings, based on by far the largest proband and relatives' samples studied with the TDI to date, provide independent confirmation of previous empirical findings and phenomenological observations of distinctive qualitative similarities between the TD found in SZ probands and in their nonschizophrenic first-degree biological relatives.[41,42,44,98] Thus, the psychotic form of the illness is not a necessary condition for the presence of TD. Rather, TD is both a symptom of SZ and a potential indicator of a genetic predisposition that becomes exacerbated after disease onset.

The selective familial aggregation of DVs in RelSZ suggests that this TD phenotype may be a pleiotropic expression of risk genes. In that case, this "cognitive biomarker" may be useful in identifying non-penetrant gene carriers among clinically unaffected RelSZ. Indeed, this is one of the key justifications for incorporating endophenotypes into genetic studies of psychiatric disorders.[140–145] Despite the highly polygenic collective contribution of common variants, the ES for individual variants are quite small.[146,147] This fact underscores the value of endophenotypes.[148–151] Endophenotypes have a role in gene discovery, either alone or in combination with diagnosis, by identifying subgroups with a particularly large genetic signal. Endophenotypes also reduce genetic heterogeneity and help to clarify the role of specific genes in disease risk; indeed, they are "essential to the interpretation of genetic findings," in part because smaller sample sizes are likely to be needed to identify loci with larger ES: "… even a small increase in the mean locus-specific effect size has a substantial impact on power…".[150] Using TDI data to illustrate, we have shown elsewhere that, for a specific sample size, a linkage analysis based on an endophenotype has much more power than one based on the disease when the penetrance of the endophenotype is much higher than that of the disease.[152]

The quantitative TD scores may be especially useful in improving the accuracy of polygenic risk scores (PGRSs) to detect non-penetrant carriers among clinically unaffected relatives. The PGRS aggregates the effects of individual risk alleles into a cumulative genetic risk estimate and can have predictive utility when a large contribution to a trait is polygenic. Although the predictive accuracy of PGRS is currently limited,[153–155] it will increase as samples get larger, more risk alleles are identified, and linkage disequilibrium is taken into account.[156–159] In addition, multivariate analysis maximizes the predictive accuracy of PGRS, showing a significant advantage to using data from multiple correlated traits.[160] Thus, using the DV TD phenotype

to define homogeneous subgroups of patients and relatives in the context of PGRS scores may distinguish between non-penetrant carriers and noncarriers of risk genes among relatives or between patients with differing degrees of polygenic risk. Including environmental factors that may interact with TD or with genetic risk may also improve predictive accuracy.[110,161–163]

The findings reported above are much more encouraging for a SZ-related TD phenotype than for a BP-related TD phenotype. This discrepancy may, in part, reflect the enhanced power of the much larger sample sizes of the SZ and RelSZ groups (the larger sample sizes of these groups reflect the recruitment strategy at the time the data were collected, as the study was designed to primarily assess TD in SZ and RelSZ, with BP and RelBP being included as psychiatric control groups). Even with comparatively smaller samples, however, the narrowly defined "BP CT" score had larger estimated ES in both the BP and RelBP groups than the CT score. Taken together, these results provide preliminary support for the relatively selective association of "BP" CT with BP, the relatively selective familial aggregation of "BP" CT in RelBP, and the *dissociation* of "BP" CT from SZ. Independent replication of these results and further refinement of this TD phenotype in larger samples of BP and RelBP is clearly warranted. It will be of interest to apply this hierarchical finite mixture model technique to subtypes of CT in whom heterogeneity may be linked to group. Conceivably, it may one day be possible to develop a *transdiagnostic* TD phenotype[164] that can be used to enhance the identification of non-penetrant SMI gene carriers.

We evaluated dimensions of TD that are most salient using the TDI. Other TD dimensions have been described and there are a number of different TD scales.[165,166] It would be potentially informative to compare the same individuals on different TD scales and to examine the longitudinal patterns of TD across scales.

Our patient sample consisted entirely of outpatients, indicating that the elevated TD we observed in these groups was not dependent on being in an acute clinical state. Although severity of TD does fluctuate with clinical state, the risk of TD false negatives is relatively low, especially in relation to SZ.[46,165,167,168] Notably, over 80% of BP patients continued to show detectable TD as outpatients, whether or not they were in full or partial remission or still met criteria for BP. Furthermore, for BP who showed some TD, subtype of most recent episode (manic, depressed, or mixed) was not significantly associated with the severity of the TD. The presence of detectable TD in substantial proportions of clinically unaffected relatives also supports the relative independence of TD from clinical state per se.

Our proband, relatives, and control groups were orders of magnitude larger than previous samples that have been studied with the TDI (at least 3 to as much as 8 times larger).[41,42,44,45,98] The findings are consistent with those previously reported for SZ and RelSZ and represent a significant advance in characterizing the TD associated with BP disorder and with its co-familiality and in clarifying the distinct characteristics of the TD profiles in the 2 proband and relatives groups.

Some NC (n = 43, 23.4%) showed either high DV scores and had at least one instance of severe TD. We reviewed all of the personal and informant material on these individuals in order to try to understand these results. Barring misrepresentation of personal or family history that would have excluded them from participating, we could find no plausible explanation. Our dataset consists entirely of cross-sectional samples of TD; it would be useful to know whether longitudinal data would show a similar pattern of findings in these individuals.

Finally, our results for TD are much more consistent with diagnostic distinctions than findings for various biological measures, whose heterogeneity seems less disease-related,[169,170] or with the substantial overlap in genetic susceptibility loci across disorders (see above). It could be especially probative to examine the patterns observed when the combined effects of such biomarkers, TD phenotypes and other cognitive markers are considered.

Supplementary Material

Supplementary data are found at *Schizophrenia Bulletin* online.

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