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Letter to the editor

Thought and language disorder as a possible endophenotype in schizophrenia: Evidence from patients and their unaffected siblings

Dear Editors,

Genetics depends on the relationship between genotypes and manifested phenotypes. Defining illness-related genes has been successful in many illnesses (i.e., Alzheimer's Disease) with homogenous symptoms and etiology. However, in some illnesses which have heterogeneous symptoms and etiology, such as schizophrenia, discovering the risk genes has been more challenging. To aid gene discovery, researchers used *endophenotypes*, quantitative biological traits that are reliable in reflecting discrete biological systems and are heritable, so they are more related to the root cause of the illness than the broad clinical factors (Preston and Weinberger, 2005). Few studies (Pawełczyk et al., 2018) have assessed thought and language (TaL) disorder as a possible endophenotype in schizophrenia. Furthermore, the data on TaL are conflicting. For example, previous literature has neglected subjectively reported symptoms and did not consider the non-independence of the observations within families nor the age difference between patients with schizophrenia and their parents/siblings and healthy controls that could affect the results of the TaL tests.

As it is crucial to define variables associated with the vulnerability markers of schizophrenia, the present study examines patients (SZ) ($N = 24$), their unaffected siblings (SIB) ($N = 24$), and a healthy control group (HC) ($N = 24$) (Demographic and clinical characteristics are summarized in Table 1 in supplementary material). We included patients from the Community Mental Health Center of Etimesgut Şehit Sait Ertürk State Hospital, who were in the 18–50 years of age range, were diagnosed with schizophrenia according to DSM-5, had a minimal education of 5 years, did not have any neurological diseases and mental retardation. An expert speech and language therapist (TÇ) who was blind to patients' clinical status tested all the participants during one session. The study was approved by the Bilkent University Ethics Committee. The aim was to comprehensively assess TaL functions as possible endophenotypes of schizophrenia using multiple scales and assessments (Table 2 in supplementary material; Thought and Language Index-TLI (Liddle et al., 2002; Ulaş et al., 2007), Thought and Language Disorder Scale-TALD (Kircher et al., 2014; Mutlu et al., 2019), Phonemic and Semantic Fluency (Lezak, 1995; Tunçer, 2011), Boston Naming Test-BNT (Kaplan et al., 1983; Ekinci Soylu and Cangöz, 2018), Scale for Scoring the Inclusion and the Quality of the Parts of the Story-SSIQPS (Harris and Graham, 1996; Coşkun, 2005)). For this aim, we used ANOVA with post-hoc pairwise comparions (Analysis 1) and multinomial logistic regression models by preferring 'cluster' in the analysis to find which tests are our groups' best predictors and discriminators. Group (SZ, SIB, and HC) was a dependent variable, and all tests which could differentiate at least one pair (i.e. SZ and HC; SIB and HC) in the results of ANOVA with post-hoc pairwise comparisons were added to the model as the independent variables (Analysis 2). In order to avoid multicollinearity, TALD and its factors were not included in this model. Instead, they were evaluated in another multinominal logistic regression model (Analysis 3).

When we examined the results of Analysis 1 (Table 3 in supplementary material), BNT, fluency tests, SSIQPS scores were significantly impaired in both SZ and SIB groups compared to HC group. TLI was significantly impaired in SZ compared to HC. TALD-TR total and factor scores showed a distinct pattern of thought disorder severity. SZ group exhibited the highest scores in the TALD-TR total score, the subjective negative, the objective negative and the subjective negative factor scores. SIB group showed milder impairment than SZ group, whereas both SZ and SIB groups significantly differed from HC. The objective positive factor score was similar between SZ and SIB group, and, as expected, higher than the HC group. In the Relative Risk Ratios (RR) of Analysis 2, we found that SZ and SIB demonstrated an overall lower level of TaL functioning compared to our reference group, healthy controls in all TaL tests except for phonemic fluency (Table 1). Besides, TaL disorder resulted in higher relative risk in SZ group and a milder but increased risk in the SIB group. However, this finding was reversed for Boston Naming Test and SSIQPS, although SZ and SIB's RRs were near each other. This could be because of our relatively low number of participants.

In parallel with the literature, the TaL disorder assessed with TLI was successful in detecting the possible risk for schizophrenia in the SIB compared to the HC group. This test score was more discriminatory than the other language tests in the model. This finding may be related to the fact that TaL tests not only focus on specific dimensions of language but also cover thought disturbances (Kircher et al., 2014). To our knowledge, this is the first study to evaluate TaL disorder with all factors using TALD in unaffected siblings of SZ. Our results of Analysis 3 showed that TALD could detect TaL disorder in SZ and in the SIB group (Supplementary Table 4). RRs were the highest for the presence of *Objective Negative* symptoms, including observable negative phenotypes such as slowed thinking and poverty of speech, related to lower syntactical complexity (Thomas et al., 1987). The second highest RRs were observed for the presence of *Subjective Negative* symptoms consisting of introspective negative phenotypes best manifested by poverty of thought and expressive speech dysfunction in both SZ and SIB groups. Schizophrenia risk level was followed by *Objective Positive* symptoms represented by disorganization such as derailment and neologism, which is discussed within the scope of damaged discourse (Kuperberg, 2010), and *Subjective Positive* symptoms with similar RRs in the multinominal regression analysis (Table 4 in supplementary material). Therefore, TaL disorder may be examined in a hierarchical pattern (1. *Objective Negative* (at the top), 2. *Subjective Negative*, 3. *Objective Positive* (at the bottom)), which the unique four-factorial structure of TALD

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Table 1
The results of thought and language tests and their associations with schizophrenia risk.

	Schizophrenia risk = 0 (Controls)	Schizophrenia risk = 1 (Siblings)				Schizophrenia risk = 2 (Patients)			
	Reference group	Wald	df	RR (%95 CI)	p	Wald	df	RR (%95 CI)	p
Thought and language									
Index	-	2.46	1	4.41 (1.35–14.42)	**<0.05**	4.83	1	17.58 (5.49–56.3)	**<0.001**
Boston Naming Test	-	−2.55	1	0.91 (0.85–0.97)	**<0.05**	−3.49	1	0.83 (0.75–0.92)	**<0.001**
SSIQPS	-	−6.45	1	0.68 (0.6–0.76)	**<0.001**	−126.1	1	0.45 (0.45–0.46)	**<0.001**
Phonemic fluency	-	0.24	1	1 (0.96–1.04)	0.8	0.25	1	1 (0.96–1.04)	0.8
Semantic fluency	-	−28.73	1	0.89 (0.88–0.9)	**<0.001**	−8	1	0.91 (0.89–0.93)	**<0.001**
	Model $\chi2 = 47.25$ $df = 5$, $p < 0.001$								

CI = confidence interval, df = degrees of freedom, $\chi2$: Chi-square, RR = relative risk ratio, SSIQPS = Scale for Scoring the Inclusion and the Quality of the Parts of the Story.
Bold values indicate significance either at level *$p<0.05$ or **$p<0.001$

could capture. In other words, this hierarchical pattern proves that *Objective Negative* symptoms have the best power to discriminate the groups from each other. This is followed by *Subjective Negative* and *Objective Positive symptoms*. Another finding in our study is that semantic verbal fluency in SIB is significantly lower than in HC group. Semantic verbal fluency is related to semantics, a subfield of linguistics. When we consider that semantics is damaged more than phonetics and phonology in SZ (Kircher et al., 2018), this result is not surprising. To the best of our knowledge, the critical contribution of this study to the TaL research field in SZ and SIB is that accessing words from the mental lexicon, naming, and *aiming to convey more information in a given context to the listeners beyond using grammatical sentences* (i.e., discourse) as indexed by the Boston Naming Test and SSIQPS scores were significantly discriminating both SZ and SIB from the HC group. SSIQPS is scored based on the stories created by the participants from the Thematic Apperception Test pictures presented to them and stories can be examined within the scope of discourse. It is known that discourse is one of the most damaged areas of language in SZ (Kircher et al., 2018). Also, Berenbaum et al. (2008) showed that the Boston Naming Test relates to discourse in SZ. We showed for the first time that a deficit in discourse is also seen in the SIB group. Although our findings support that TaL could be a possible endophenotype in SZ, the mean age of the siblings (*M*: 37, *SD*: 7.91) is relatively high to develop SZ and we do not have evidence that disease-related genes mediate the similarity in performance between the SZ and SIB groups. Still, our findings are consistent with the SZ sibling literature on general cognition that suggests that deficits in siblings are likely to reflect inherited vulnerability.

Our results showed that thought and especially semantics, pragmatics/discourse, and naming as subparts of language could be possible endophenotypes in SZ. Thus, their assessment may improve the early diagnosis of the illness and comprehension of its pathophysiology. Besides, some TaL tests, which are well validated, easy to use, and not time-consuming, can be more effective than the others in discriminating the SIB group from HC.

CRediT authorship contribution statement

Conceived and designed the experiments: TT&TÇ. Collected data: TÇ, EM. Analyzed data: TÇ. Wrote the first draft of the paper: TÇ. Contributed to and critically reviewed the manuscript: TT, EM.

Declaration of competing interest

None of the authors has any conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.02.005.

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