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ORIGINAL PAPER

Higher order theory of mind in patients with bipolar disorder and schizophrenia/schizoaffective disorder

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Abstract

Some evidence suggests that patients with bipolar disorder (BD) have better Theory of Mind (ToM) skills than patients with schizophrenia/schizoaffective disorder (SCH). However, this difference is not consistently reported across studies, so rather than being global, it may be restricted to specific aspects of ToM. Our primary objective was to compare higher order ToM performance between BD and SCH patients using the Hinting Task (HT). Ninety-four remitted patients were recruited (BD = 47, SCH = 47). Intelligence quotient (IQ), attention, memory, executive functions, and processing speed were also assessed. Patients with BD performed better on the HT than patients with SCH, even when the analysis was adjusted for IQ and neurocognition ($p < 0.001$, $\eta_p^2 = 0.144$). Regression analysis in the total sample showed that a diagnosis of SCH and lower IQ were associated with lower HT scores ($R^2 = 0.316$, $p < 0.001$). In the BD group, verbal memory and processing speed were the main predictors of HT performance ($R^2 = 0.344$, $p < 0.001$). In the SCH group, no variable was significant in explaining HT performance. In the context of previous studies that found no significant differences in the most basic aspects of ToM (e.g., understand other people's thoughts/beliefs), our results suggest that differences between the two disorders might be limited to the more challenging aspects (e.g., understand the intended meaning of indirect requests). No causal inferences can be made in this cross-sectional study. However, regression analyses show that whereas in BD patients, ToM functioning would be partially modulated by neurocognitive performance, in SCH patients, it could be largely independent of the well-known neurocognitive impairment.

Keywords Bipolar disorder · Schizophrenia · Remission · Neurocognition · Theory of mind · Hinting task

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Introduction

"Theory of Mind" (ToM) encompasses the ability to understand the cognitive and affective mental states of oneself and others and the ability to use this knowledge to predict and anticipate people's behavior [1]. Patients with bipolar disorder (BD) and schizophrenia/schizoaffective disorder (SCH) show mild-to-severe deficits in ToM throughout the course of the disease, including the prodromal, acute, and remitted phases [2, 3]. Although less severe, similar difficulties have been observed in their unaffected first-degree relatives, suggesting some degree of heritability and that ToM difficulties are a vulnerability marker for BD and SCH [4, 5].

ToM is more closely related to social functioning than most clinical and neurocognitive variables. Therefore, an intact ToM is essential for adequate performance at work and in the community [6, 7]. However, it is not a monolithic function. Instead, it consists of several sub-processes among which the first-order ToM (i.e., the ability to know what another person thinks or believes), the second-order ToM (i.e., the ability to know what a person thinks that another person thinks or believes) and other forms of higher order ToM (e.g., understand sarcasm, metaphors or indirect requests) stand out [8].

Most research agrees that patients with BD have better ToM skills than patients with SCH [9, 10]. However, some studies have found no differences in first- and second-order ToM, especially when assessed by classic false-belief tasks [11, 12]. On one hand, this finding suggests that differences in ToM may be subtler than previously thought, such that patients with BD and SCH may perform similarly in the most basic aspects (i.e., first- and second-order ToM), but differently in the more advanced ones (i.e., higher order ToM) [10]. On the other hand, false-belief tasks are known to be among the easiest ToM tests to solve, so they might not be sensitive enough to detect subtle differences in this cognitive domain [13]. To overcome this limitation, the Social COgnition Psychometric Evaluation (SCOPE) study emphasized the need to use more complex and sophisticated tests [14], such as the Hinting Task (HT) [15].

The HT is a higher order ToM test that was originally designed for SCH patients but has also been used in BD patients [13]. To date, only five studies in patients with BD and SCH have explored higher order ToM using the HT, three of which found significant differences between the groups [11, 16, 17] and two found similar functioning between them [18, 19]. This lack of consistency across studies may be determined by several confounding factors, such as the clinical status and neurocognitive functioning of patients and, in subjects with BD, by the presence of psychotic characteristics [9, 10].

Regarding the clinical status of the patients, remission seems to be the most convenient state to examine ToM performance [20]. Indeed, two of the three studies that found differences between BD and SCH patients using the HT included remitted subjects [11, 16]. In patients with BD, a meta-analysis found that the severity of ToM impairment increased as symptoms worsened [21]. Similar results have been reported in patients with SCH [22]. Furthermore, there is evidence that during the acute phase of the disease, the influence of neurocognition may be masked by the impact of clinical variables. In contrast, during clinical remission, general intellectual impairment and neurocognitive deficits appear to modulate ToM performance [2, 22].

In view of this latter finding, remission would be the most convenient clinical state to examine the relationship between ToM and neurocognition. However, of the five studies mentioned in which the HT was used, only two studies involving remitted subjects explored the impact of executive functions on higher order ToM, providing mixed results [11, 16], while no study investigated the influence of other neurocognitive domains such as attention, memory and processing speed.

Finally, we know of only one study in patients with BD and SCH that has explored the impact of psychotic characteristics on ToM performance using the HT [19] and found no differences between BD patients with and without a history of psychosis and SCH patients. However, some of the patients in this study suffered from mild mood symptoms. Recent evidence suggests that depressive symptoms adversely affect ToM performance [2, 7], further emphasizing the need for studies in symptom-free subjects.

An in-depth assessment of high-order ToM in symptom-free patients with BD and SCH, as well as the identification of specific modulatory factors, is an unmet need that will allow a better characterization of the ToM capacity of these disorders. In this study, we attempted to overcome some of the limitations of previous research by including only remitted subjects, using an advanced ToM test, and employing a comprehensive neuropsychological battery.

Our hypotheses were that BD patients will perform better than SCH patients on higher order ToM and that general intelligence and neurocognition will modulate ToM performance. Our primary objective was to compare higher order ToM performance between BD and SCH patients using the HT. Second, we aimed to analyze the impact of clinical variables, general intelligence and neurocognition on ToM performance.

Methods

Participants and procedure

Forty-seven patients with BD and 47 patients with SCH, matched for age, sex, and years of education, participated

in this cross-sectional study. Patients were consecutively recruited at the psychiatric clinic of the Parc Taulí University Hospital in Sabadell, Catalonia (Spain), between 2016 and 2018. All subjects had been on outpatient follow-up treatment for at least 6 months prior to enrollment and had not suffered any exacerbation of symptoms during this period.

Inclusion criteria for patients with BD were: diagnosis of BD type 1 or 2 (DSM-IV-TR criteria) [23], score of < 7 on the Young Mania Rating Scale (YMRS) [24] and score < 8 on the Hamilton Depression Rating Scale (HAM-D) [25]. For patients with SCH, the inclusion criteria were: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV-TR criteria), score of < 4 on items P1 (delusions), P2 (conceptual disorganization) and P3 (hallucinatory behavior) of the Positive and Negative Syndrome Scale (PANSS) [26] and score of < 4 on the Calgary Depression Scale for Schizophrenia (CDSS) [27].

Patients were excluded if they met any of the following criteria: age < 18 or > 64 years, any change in antipsychotic or mood stabilizer/anticonvulsant medication during the past month, any concomitant Axis I or II disorder, substance abuse or dependence in the past 6 months (excluding nicotine and caffeine), any medical or neurological disorder associated with cognitive impairment (including brain injury), electroconvulsive therapy during the past year, or intelligence quotient (IQ) ≤ 70.

The study was approved by the local Ethics Committee (#2017/579) and was carried out in accordance with the latest version of the Declaration of Helsinki. All subjects were informed about the characteristics of the study and gave written informed consent prior to enrollment. To confirm inclusion/exclusion criteria [28, 29], we reviewed electronic medical records and interviewed all patients using a semi-structured clinical interview based on DSM-IV-TR criteria. During this interview, we also collected the sociodemographic data and performed the clinical assessment. The cognitive assessment was performed in a second session. All evaluations were performed in a fixed order by experienced psychiatrists and neuropsychologists.

Clinical evaluation

Patients with BD were evaluated using YMRS and HAM-D. Patients with SCH were evaluated using PANSS and CDSS. In patients with SCH, CDSS was used instead of HAM-D, because it discriminates better between depressive and negative symptoms [30]. Age of onset, duration of illness, number of episodes and hospitalizations, history of psychosis (only in BD patients), history of drug use and prescribed psychotropic medication were also collected. In addition, daily doses of antipsychotics were converted to chlorpromazine equivalents [31], antidepressants to fluoxetine equivalents [32] and benzodiazepines to diazepam equivalents [33].

Neurocognitive evaluation

Patients were administered a battery of seven neurocognitive tests that provided fourteen neuropsychological measurements, mostly corresponding to those of the International Society for Bipolar Disorders-Battery for Assessment of Neurocognition [34] and the MATRICS Consensus Cognitive Battery for clinical trials in SCH [35]. The raw scores of all neuropsychological measurements were converted to T-scores using the normative data set provided by each test [36–39] and then averaged to create a global neurocognitive score and four neurocognitive indexes: attention/working memory, verbal memory, executive functions and processing speed (Table 1). The WAIS-III Vocabulary subtest was used to estimate the patients' premorbid IQ, as it is highly correlated with general intelligence ($r = 0.80$) [40].

High-order ToM evaluation

Higher order ToM was evaluated using the HT [15]. In this test, participants have to demonstrate their

Table 1 Neurocognitive tests that compose each neurocognitive index and its internal consistency

Neurocognitive index	Neurocognitive tests and formula for calculating the index	Cronbach's alpha
Attention/Working memory	(WAIS-III Digit Span Forward + WAIS-III Digit Span Backward + WAIS-III Arithmetic subtest + CPT-II Detectability (d') score)/4	0.610
Verbal memory	(WMS-III Logical Memory I subtest—Learning Slope + WMS-III Logical Memory II subtest—Delayed Recall)/2	0.658
Executive functions	(WCST Number of Completed Categories + TMT-part B + Stroop test Word-Color component + FAS)/4	0.759
Processing speed	(WAIS-III Digit Symbol-Coding subtest + TMT-part A + Stroop test Word-Reading component + Animal naming)/4	0.742
Global neurocognition	(Sum of all neuropsychological measurements)/14	0.836

WAIS-III Wechsler Adult Intelligence Scale-III, *CPT-II* Continuous Performance Test-II, *WMS-III* Wechsler Memory Scale-III, *WCST,* Wisconsin Card Sorting Test, *TMT* Trail Making Test, *FAS* phonemic verbal fluency, *Animal naming* semantic verbal fluency

understanding of indirect speech by answering one or two ToM questions. First, the examiner reads each story aloud and the participant listens to it until he/she has understood it. Then, the examiner asks the ToM question. If the participant's answer is correct, he/she receives 2 points; if not, information is added to make the hint clearer. If the participant's answer is correct on this second occasion, he/she receives 1 point. However, an incorrect answer is scored as 0. Although the SCOPE study suggests the use of the original version of 10-stories [14], in the present study we used the reduced version of 5-stories, because the Cronbach's alpha data from the Spanish validation study recommend it (0.69 vs. 0.78) [41]. The total score ranges from 0 to 10. A higher score means a better identification of the intended meaning of indirect requests.

Statistical analysis

All analyses were performed using SPSS v19.0. Statistical significance was set at $p < 0.05$. The normal distribution of the data was examined by visual (histogram, boxplot, and normal *Q–Q* plot) and analytical methods (skewness and kurtosis tests). Details on the normal distribution of the HT variable are shown in Online Resource 1 (see Supplementary Information, SI).

The Student's *t* test or the Mann–Whitney *U* test was used to explore differences between patients with BD and SCH in continuous variables, as appropriate. For qualitative variables, the Chi-square (X^2) test was used. Analyses exploring neurocognition and higher order ToM were adjusted for premorbid IQ. Higher order ToM was also adjusted for global neurocognition. Effect sizes based on Cohen's *d* or partial eta squared (η_p^2) are reported for all significant cognitive outcomes.

The impact of clinical variables, general intelligence and neurocognition on ToM performance (HT score) was explored separately in the total sample, the BD group and the SCH group using a series of bivariate linear regression analyses. Age and sex were also included in these analyses because of their clinical relevance to ToM performance [13, 42]. All variables that reached statistical significance in these screening analyses were included as possible factors in their corresponding multiple linear regression model (one for each of the three groups). To obtain more consistent models, non-significant variables were excluded step by step, starting with the parameters with the highest *p* value. To control the stability of the models, several properties of interest were investigated. A final model was constructed for each of the three groups that included all variables that independently influenced the HT score.

Results

Sample characteristics

Table 2 summarizes the sociodemographic, clinical, and neurocognitive characteristics of the sample. Approximately half of the patients were women (48.9%). Mean age was 46 years and mean education was 11 years. Patients with BD had a higher premorbid IQ, younger age of onset, longer duration of the disease, and higher number of total episodes than patients with SCH. In contrast, SCH patients received higher doses of antipsychotics than BD patients. Details on drug use history are shown in Online Resource 2 (see SI). BD patients performed significantly better than SCH patients in global neurocognition, verbal memory and processing speed, but not in the domains of attention/working memory and executive functions. After adjusting for premorbid IQ, only the difference in verbal memory was maintained [$F_{(1,91)} = 5.474$, $p = 0.021$] with a small-to-medium effect size ($\eta_p^2 = 0.057$), whereas it disappeared for global neurocognition ($p = 0.353$) and processing speed ($p = 0.928$).

Higher-order ToM performance

Figure 1 shows that patients with BD performed significantly better on the HT than patients with SCH [8.2 ± 1.5 vs. 6.0 ± 2.1, $t_{(82.5)} = -6.129$, $p < 0.001$, $d = 1.206$]. This difference remained after adjusting the analysis for premorbid IQ and global neurocognition [$F_{(1,90)} = 15.136$, $p < 0.001$] with a large effect size ($\eta_p^2 = 0.144$).

Additionally, we conducted an exploratory analysis in which be compared the HT performance of the patient groups in our study with that of the healthy control group of the Spanish validation study of the HT [41]. The results suggest that both BD and SCH patients perform significantly worse on the HT than healthy subjects ($p < 0.001$; $d = 0.970$ and 2.105, respectively). Further details are provided in Online Resource 3.

Impact of sociodemographic, clinical, and neurocognitive variables on higher order ToM performance

Bivariate linear regressions on the total sample showed that group, premorbid IQ, duration of illness, number of episodes, verbal memory, executive functions, and processing speed had statistically significant effects on HT performance. All other variables had $p \geq 0.05$ and were discarded. In the multiple linear regression model, group was included as a factor and all other significant variables as covariates (Table 3). Non-significant variables were

Table 2 Sociodemographic, clinical, and neurocognitive characteristics of the sample ($N = 94$)

Means (SDs) are reported unless otherwise specified			
	Patients with BD	Patients with SCH	Statistics
N	47	47	
Age (years)	47.2 (9.2)	45.2 (8.3)	$U = 913.5$, $p = 0.149$
Sex (males), *n (%)*	24 (51.1)	24 (51.1)	$X^2_{(1)} = 0.000$, $p = 1.000$
Education (years)	11.5 (2.5)	10.6 (2.5)	$U = 861.0$, $p = 0.062$
Premorbid IQ[a]***	99.6 (7.5)	87.1 (9.9)	$t_{(85.6)} = -6.881$, $p < 0.001$
Bipolar disorder type 1/2, *n*	39/8		
Schizophrenia/Schizoaffective disorder, *n*		31/16	
YMRS total score	0.8 (1.4)		
HAM-D total score	3.8 (2.2)		
PANSS total score		52.7 (13.1)	
Positive subscale		10.0 (3.3)	
Negative subscale		17.2 (5.8)	
General subscale		25.6 (5.9)	
CDSS total score		1.3 (1.3)	
Age of onset (years)**	26.6 (10.1)	32.0 (8.7)	$U = 705.0$, $p = 0.003$
Duration of illness (years)***	20.6 (11.4)	11.5 (9.2)	$U = 584.0$, $p < 0.001$
Number of hospitalizations	1.9 (2.0)	2.0 (2.6)	$U = 1060.0$, $p = 0.728$
Number of episodes***	8.5 (5.2)	2.7 (2.6)	$U = 238.5$, $p < 0.001$
Manic episodes	2.0 (1.7)		
Hypomanic episodes	2.0 (2.8)		
Depressive episodes	4.0 (2.7)		
Mixed episodes	0.5 (1.0)		
History of psychosis, *n* (%)	28 (60.0)		
Antipsychotics only (AP), *n* (%)***	0 (0.0)	15 (32.0)	$X^2_{(1)} = 17.848$, $p < 0.001$
Mood Stabilizers/Anticonvulsants only, *n* (%)	3 (6.0)	0 (0.0)	$X^2_{(1)} = 3.099$, $p = 0.078$
AP + Mood Stabilizers/Anticonvulsants only, *n* (%)*	13 (28.0)	5 (11.0)	$X^2_{(1)} = 4.398$, $p = 0.036$
Other combinations (including AD + BZD), *n* (%)	31 (66.0)	27 (57.0)	$X^2_{(1)} = 0.720$, $p = 0.396$
Chlorpromazine equivalents (mg/d)***	219.2 (251.3)	539.5 (406.6)	$U = 382.5$, $p < 0.001$
Fluoxetine equivalents (mg/d)	38.3 (19.5)	42.2 (26.6)	$U = 216.5$, $p = 0.830$
Diazepam equivalents (mg/d)	20.0 (13.3)	20.2 (12.2)	$t_{(38)} = 0.059$, $p = 0.969$
Global neurocognition[b,]*	44.9 (5.2)	42.7 (5.3)	$t_{(92)} = -2.060$, $p = 0.042$
Attention/Working memory[b]	45.0 (6.0)	45.1 (6.4)	$t_{(92)} = 0.076$, $p = 0.939$
Verbal memory[b,]***	47.8 (7.8)	40.9 (6.5)	$t_{(92)} = -4.680$, $p < 0.001$
Executive functions[b]	41.8 (8.6)	40.5 (7.4)	$t_{(92)} = -0.787$, $p = 0.434$
Processing speed[b,]*	46.4 (6.2)	43.4 (6.3)	$t_{(92)} = -2.383$, $p = 0.019$

SD Standard deviation, *BD* Bipolar disorder, *SCH* Schizophrenia/Schizoaffective disorder, *IQ* Intelligence quotient, *YMRS* Young Mania Rating Scale, *HAM-D* 17-item Hamilton Depression Rating Scale, *PANSS* Positive and Negative Syndrome Scale, *CDSS* Calgary Depression Scale for Schizophrenia, *AD* Antidepressants, *BZD* Benzodiazepines

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a]Premorbid IQ is presented in standard scores (mean ± SD = 100 ± 15)

[b]Neurocognitive variables are presented in T-scores (mean ± SD = 50 ± 10)

extracted from the model in the following order: duration of illness ($p = 0.951$), processing speed ($p = 0.747$), number of episodes ($p = 0.452$), executive functions ($p = 0.221$) and verbal memory ($p = 0.084$). The final model included group (B = 1.662, 95% CI 0.78–2.55, $p < 0.001$) and premorbid IQ (B = 0.049, 95% CI 0.01–0.09, $p = 0.020$) and explained 31.6% of the variance of the HT score [non-adjusted $R^2 = 0.331$, $F_{(2,91)} = 22.507$, $p < 0.001$]. Further details are provided in Online Resource 4 (see SI).

Bivariate linear regressions in the BD group showed that verbal memory, executive functions, and processing speed had statistically significant effects on HT performance. All

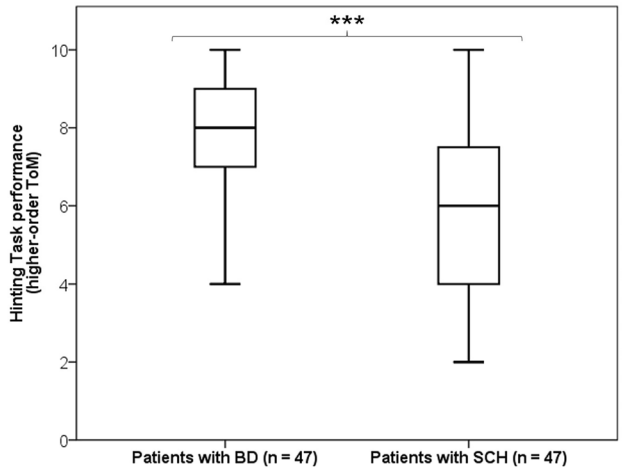

Fig. 1 Comparison of higher-order ToM performance between BD and SCH patients ($n=94$). *ToM* Theory of Mind, *BD* Bipolar disorder, *SCH* Schizophrenia/Schizoaffective disorder. Boxplots showing the median (bold line), minimum and maximum values (whiskers), and the first and third quartiles (middle lines between the bold line and the whiskers) of the Hinting Task score in each of the two group. Results are presented in raw scores. Further details are provided in Online Resource 1. ***$p<0.001$

other variables (including diagnostic subtype and history of psychosis) had $p \geq 0.05$ and were discarded. In the multiple linear regression model, verbal memory and processing speed, but not executive functions, remained significant factors (Table 4). The final model included verbal memory (B = 0.073, 95% CI 0.026–0.120, $p=0.003$) and processing speed (B = 0.089, 95% CI 0.030–0.148, $p=0.004$) and explained 34.4% of the variance of the HT score [non-adjusted $R^2=0.373$, $F_{(2,44)}=13.084$, $p<0.001$]. Further details are provided in Online Resource 4 (see SI).

In the SCH group, only premorbid IQ showed a trend towards significance. All other variables (including diagnostic subtype and PANSS Negative) had $p \geq 0.05$ and were discarded (Table 4). Therefore, multiple linear regression analysis was not performed.

Discussion

Our results show that patients with BD performed significantly better on higher order ToM than patients with SCH, corroborating the findings of previous studies [9, 10]. In the total sample, SCH diagnosis and lower premorbid IQ were associated with worse performance on higher order ToM. However, this result changed when the analysis was conducted separately for the BD and SCH groups, suggesting that, at least during remission, the factors underlying ToM performance might differ between the two disorders. Specifically, whereas in BD patients, higher order ToM would be partially modulated by neurocognitive functioning, in SCH patients, no variable proved significant in explaining its performance, possibly reflecting that higher order ToM is largely independent of the well-known neurocognitive impairment that characterizes this clinical population.

Our findings may help to understand why previous studies using classic false-belief tasks found no differences in

Table 3 Impact of sociodemographic, clinical, and neurocognitive variables on higher order ToM performance (HT score) in the whole sample ($N=94$)

	Bivariate linear regressions		Multiple linear regression model	
	B (95% CI)	*p*	B (95% CI)	*p*
Group**	**2.277 (1.54 to 3.01)**	**< 0.001**	**1.414 (0.38 to 2.45)**	**0.008**
Age	0.037 (− 0.01 to 0.09)	0.137		
Sex	− 0.017 (− 0.89 to 0.86)	0.969		
Premorbid IQ	**0.095 (0.06 to 0.13)**	**< 0.001**	0.028 (− 0.02 to 0.08)	0.250
Age of onset	− 0.024 (− 0.07 to 0.02)	0.295		
Duration of illness	**0.050 (0.01 to 0.09)**	**0.009**	0.001 (− 0.04 to 0.04)	0.951
Number of episodes	**0.165 (0.08 to 0.25)**	**< 0.001**	0.031 (− 0.07 to 0.14)	0.555
Chlorpromazine equivalents	− 0.001 (− 0.01 to 0.01)	0.140		
Fluoxetine equivalents	0.002 (− 0.03 to 0.03)	0.917		
Diazepam equivalents	0.002 (− 0.05 to 0.06)	0.942		
Attention/working memory	0.023 (− 0.05 to 0.09)	0.522		
Verbal memory	**0.111 (0.06 to 0.16)**	**< 0.001**	0.037 (− 0.02 to 0.09)	0.189
Executive functions	**0.064 (0.01 to 0.12)**	**0.018**	0.024 (− 0.04 to 0.01)	0.482
Processing speed	**0.104 (0.04 to 0.17)**	**0.002**	0.014 (− 0.07 to 0.10)	0.746

ToM Theory of Mind, *HT* Hinting Task, *BD* Bipolar disorder, *SCH* Schizophrenia/Schizoaffective disorder, *IQ* Intelligence quotient

Statistically significant results are in bold

**$p<0.01$ in the multiple linear regression model

Table 4 Impact of sociodemographic, clinical, and neurocognitive variables on higher-order ToM performance (HT score) in BD and SCH groups

	Patients with BD ($N=47$)				Patients with SCH ($N=47$)	
	Bivariate linear regressions		Multiple linear regression model		Bivariate linear regressions	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Age	0.035 (− 0.01 to 0.08)	0.142			0.007 (− 0.07 to 0.08)	0.844
Sex	0.308 (− 0.56 to 1.17)	0.477			− 0.342 (− 1.58 to 0.89)	0.579
Premorbid IQ	0.038 (− 0.02 to 0.10)	0.184			0.056 (− 0.01 to 0.12)	0.073
Diagnostic subtype	0.321 (− 0.83 to 1.47)	0.578			1.102 (− 0.26 to 2.83)	0.116
PANSS Negative					− 0.086 (− 0.19 to 0.02)	0.103
Age of onset	0.034 (− 0.08 to 0.08)	0.114			− 0.023 (− 0.09 to 0.05)	0.519
Duration of illness	− 0.004 (− 0.04 to 0.03)	0.832			0.034 (− 0.03 to 0.10)	0.307
Number of episodes	0.014 (− 0.07 to 0.10)	0.743			0.186 (− 0.05 to 0.42)	0.115
History of psychosis	− 0.314 (− 1.19 to 0.57)	0.476				
Chlorpromazine equivalents	− 0.001 (− 0.01 to 0.01)	0.143			0.001 (− 0.01 to 0.01)	0.271
Fluoxetine equivalents	− 0.023 (− 0.05 to 0.01)	0.143			0.030 (− 0.01 to 0.07)	0.117
Diazepam equivalents	− 0.010 (− 0.07 to 0.05)	0.705			0.016 (− 0.07 to 0.10)	0.683
Attention/Working memory	0.045 (− 0.03 to 0.12)	0.212			0.006 (− 0.09 to 0.10)	0.897
Verbal memory***	**0.093 (0.04 to 0.14)**	**< 0.001**	**0.074 (0.03 to 0.12)**	**0.003**	0.011 (− 0.09 to 0.12)	0.815
Executive functions	**0.060 (0.01 to 0.11)**	**0.014**	− 0.008 (− 0.07 to 0.05)	0.785	0.043 (− 0.04 to 0.13)	0.305
Processing speed*	**0.114 (0.05 to 0.18)**	**0.001**	**0.096 (0.02 to 0.18)**	**0.021**	0.017 (− 0.08 to 0.12)	0.734

ToM Theory of Mind, *HT* Hinting Task, *BD* Bipolar disorder, *SCH* Schizophrenia/Schizoaffective disorder, *IQ* Intelligence quotient, *PANSS* Positive and Negative Syndrome Scale

Statistically significant results are in bold

*$p < 0.05$ in the multiple linear regression model, ***$p < 0.01$ in the multiple linear regression model

first- and second-order ToM between BD and SCH patients [11, 12]. As mentioned at the beginning of the manuscript, false-belief tasks are relatively simple tests that require a very low cognitive workload to be successfully solved. In contrast, the HT is a more complex and sophisticated test, considered more sensitive for detecting subtle deficits in ToM [13, 14]. From this perspective, it can be concluded that patients with BD and SCH might perform similarly in the basic ability to infer the thoughts and beliefs of others (i.e., first- and second-order ToM), but differently in the advanced ability to understand the intended meaning of indirect requests (i.e., higher-order ToM). Other studies involving healthy subjects found evidence of intact first- and second-order ToM and impaired higher order ToM in both disorders (compared with the healthy control group) [4, 43]. This is consistent with the hypothesis that, at least during remission, differences between BD and SCH patients would not be global but restricted to the most challenging aspects of ToM [10]. However, there is evidence that the severity of ToM impairment increases as mood and/or psychotic symptoms worsen [21, 22]. Therefore, it is possible that the use of different remission criteria partly explains the divergent results between our work and other studies that also used the HT but found no differences in higher order ToM [18, 19]. In this sense, an effort should be made to reach a consensus. Indeed, considering previous evidence that mild depressive symptoms negatively affect ToM performance [2, 7], we advocate the establishment of remission criteria that include not only mania and positive and negative psychotic symptoms, but also concomitant depressive symptoms.

As expected, regression analysis on the total sample showed that higher order ToM was related to group differences in general intelligence. However, it is noteworthy that the difference between BD and SCH patients in ToM remained even after adjusting the analysis for premorbid IQ. In view of this result, we can largely rule out that the better ToM performance of BD patients simply reflects group differences in this variable. At the same time, higher order ToM was not related to group differences in clinical course variables, psychotropic medication, or neurocognitive functioning. A meta-analysis of longitudinal studies exploring neurocognition (not including social cognition) in BD and SCH found that cognitive deficits tend to remain fairly stable over the course of the disease in most patients [44]. However, a recent cross-sectional study using the HT reported worse higher order ToM performance in advanced stages of SCH compared to early stages [45], thus empathizing the need for longitudinal studies that explore in more detail whether ToM difficulties evolve differently in these disorders.

In BD patients, poorer verbal memory and slower processing speed were associated with worse higher order ToM performance. The executive functions domain, which included measures of abstract reasoning, set-shifting abilities, inhibitory control, and phonemic verbal fluency, was not related to ToM performance. This contrasts with previous research in which abstract reasoning, set-shifting abilities, inhibitory control, and planning skills emerged as the main predictors of ToM performance [16, 46, 47]. Instead, our results agree with those of Lindgren et al. [48], who showed that verbal memory and processing speed would be its main determinants. However, it should be noted that Duff et al. [49] revealed that there is considerable overlap between tests of logical memory and executive functions, as shown by a shared variance of 50–60%. Therefore, given that we used this type of memory tests in our study, we cannot completely rule out a possible role of executive functions that future research should address in more detail.

In SCH patients, no clinical or neurocognitive variable was related to higher order ToM performance. On one hand, this result is consistent with previous studies in remitted patients with SCH in which ToM impairment was independent of the well-known neurocognitive dysfunction [11, 50]. However, this finding has not been consistently replicated across studies [16, 22, 51], so further research is needed to draw definitive conclusions about whether and to what extent neurocognitive functioning in this clinical population modulates ToM functioning. On the other hand, we may have missed appropriate predictors, such as cognitive reserve [52] and childhood trauma, particularly physical neglect and sexual abuse [53, 54], which previous studies have shown to be related to social cognitive performance. Therefore, caution is advised when interpreting the results of this regression analysis.

Compared to previous studies exploring higher order ToM using the HT [11, 16–19], our work has several strengths, including a sizable sample, restricted remission criteria, and/or a comprehensive neuropsychological battery. However, we acknowledge as a limitation the lack of a healthy control group. In an attempt to overcome this limitation, we compared the HT performance of the patient groups in our study with that of the healthy control group of the Spanish validation study of the HT [41]. The results of this analysis suggest that both BD and SCH patients suffer higher order ToM deficits compared to healthy subjects. Interestingly, the effect sizes of these differences were similar to those in previous literature [14, 21, 22, 55], thus reinforcing the value of this exploratory analysis. These data are consistent with previous research showing that BD patients would perform intermediate between healthy subjects and SCH patients [9, 10]. Also, with other studies according to which ToM difficulties could be a trait-dependent impairment of SCH [5] and, possibly, BD [4, 46, 56]. However, the participants in the healthy control group were younger than the patients in our study. There is evidence that ToM functioning worsens with age [13]. Consequently, although age was not related to higher order ToM functioning either in our study or in the Spanish validation study of the HT, the results of this analysis should be considered merely informative and for hypothesis-generating purposes only.

Limitations

In addition to the lack of a healthy control group, other limitations would be the cross-sectional design, which does not allow any causal inference, and that the neuropsychologists were not blind to the psychiatric diagnosis. The inclusion of patients with BD type 2 and schizoaffective disorder may also be a limitation of the study, as other research has found better cognitive outcomes (not including ToM) in these patients than in those with BD type 1 and schizophrenia [57, 58]. However, given that diagnostic subtype was not significant in the regression analyses, we can largely rule out a possible confounding effect of this variable on higher order ToM. Nevertheless, considering new findings that point to a continuum between schizophrenia, schizoaffective disorder, and bipolar disorder with and without psychotic features, researchers should not disregard dimensional approaches to mental illness when exploring ToM functioning in future studies [59]. Finally, it should be noted that patients with SCH were taking higher doses of chlorpromazine equivalents than patients with BD. Antipsychotic and antidepressant drugs are known to have an anticholinergic effect that could adversely affect cognitive performance [60]. Unfortunately, discontinuation or modification of drug treatment was not warranted in this study. Therefore, their possible impact on higher order ToM was examined using linear regressions. The results of these analyses show that neither antipsychotics, antidepressants nor benzodiazepines influenced ToM performance.

Conclusion

Our results show that patients with BD perform significantly better on higher order ToM than patients with SCH, independent of group differences in other neurocognitive domains, but that general intelligence influences this difference. Contextualized in the current literature, the present findings suggest that the differences between the two disorders may be subtler than previously thought, mainly affecting the more complex and sophisticated aspects of ToM. As clinical implications, both groups of patients could benefit from rehabilitation interventions designed to improve cognitive functioning. However, whereas BD patients would benefit from rehabilitation of verbal memory and processing

speed [61], in SCH patients, additional effort should be made to rehabilitate the more challenging aspects of ToM [62]. Our findings also have practical implications for how we should communicate with patients with BD and, especially, SCH. Ambiguity, irony, and the use of double meanings are frequent sources of misunderstanding and should be avoided.

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Author contributions MJ and NC designed the study and wrote the protocol. GNV, JC and JMC recruited the patients and conducted the clinical assessment. GNV, MVG, MSB and SFG conducted the cognitive assessment. GNV, XG and NC run the statistical analysis. GNV drafted the first version of the manuscript. All authors contributed to data interpretation, critically reviewed the article for important intellectual content, approved the final version for publication, and participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Availability of data The data that support the findings of the study can be obtained from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval The study was approved by the Ethics Committee of the Parc Taulí University Hospital in Sabadell, Catalonia (Spain) (#2017/579), and was conducted in accordance with the principles of the Declaration of Helsinki of 1964 and its subsequent amendments.

Consent to participate All patients gave written informed consent prior to inclusion in the study.

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