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Group and sex differences in social cognition in bipolar disorder, schizophrenia/schizoaffective disorder and healthy people

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ABSTRACT

Background: Impairment of social cognition is documented in bipolar disorder (BD) and schizophrenia/schizoaffective disorder (SCH). In healthy individuals, women perform better than men in some of its sub-domains. However, in BD and SCH the results are mixed. Our aim was to compare emotion recognition, affective Theory of Mind (ToM) and first- and second-order cognitive ToM in BD, SCH and healthy subjects, and to investigate sex-related differences.

Methods: 120 patients (BD = 60, SCH = 60) and 40 healthy subjects were recruited. Emotion recognition was assessed by the Pictures of Facial Affect (POFA) test, affective ToM by the Reading the Mind in the Eyes Test (RMET) and cognitive ToM by several false-belief stories. Group and sex differences were analyzed using parametric (POFA, RMET) and non-parametric (false-belief stories) tests. The impact of age, intelligence quotient (IQ) and clinical variables on patient performance was examined using a series of linear/logistic regressions.

Results: Both groups of patients performed worse than healthy subjects on POFA, RMET and second-order false-belief ($p < 0.001$), but no differences were found between them. Instead, their deficits were related to older age and/or lower IQ ($p < 0.01$). Subthreshold depression was associated with a 6-fold increased risk of first-order false-belief failure ($p < 0.001$). Sex differences were only found in healthy subjects, with women outperforming men on POFA and RMET ($p \leq 0.012$), but not on first/second-order false-belief.

Limitations: The cross-sectional design does not allow for causal inferences.

Conclusion: BD and SCH patients had deficits in emotion recognition, affective ToM, and second-order cognitive ToM, but their performance was comparable to each other, highlighting that the differences between them may be subtler than previously thought. First-order cognitive ToM remained intact, but subthreshold depression altered their normal functioning. Our results suggest that the advantage of healthy women in the emotional and affective aspects of social cognition would not be maintained in BD and SCH.

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1. Introduction

Social cognition, defined as the ability to recognize, understand, and interpret one's own and others' emotions, thoughts, beliefs, and feelings [1], is crucial for successful functioning at work and in the community [2,3]. In patients with bipolar disorder (BD) and schizophrenia/schizoaffective disorder (SCH), mild to severe deficits in this domain have been described throughout the course of the illness, including phases of clinical stability [4,5]. There is evidence that these deficits tend to remain fairly stable in most patients [6,7]. However, variables such as age, general intelligence, residual symptoms, psychotropic drugs and, in BD patients, history of psychosis, may modulate their severity [8–12].

Social cognition is a multidimensional construct that includes different sub-domains, namely emotional processing, Theory of Mind (ToM), social perception, social knowledge, and attributional bias. Within these sub-domains, facial emotion recognition (emotional processing), mental state decoding (ToM) and mental state reasoning (ToM) have been the most explored functions so far [1,4–6], and are considered three of the main predictors of social functioning [2,3]. In addition, they are key domains of the ISBD Battery for Assessment of Neurocognition [13] and the MATRICS Consensus Cognitive Battery [14] and have recently been included as treatment targets in both disorders [15].

In healthy individuals, sex plays a crucial role in emotion recognition and ToM, which, in turn, can be dissociated into two independent but interacting processes [1,16]: *affective* ToM (decoding of complex emotions, i.e., feelings) and *cognitive* ToM (reasoning about thoughts and beliefs). In general, studies agree that women tend to perform better than men in emotion recognition and affective ToM. However, the extent to which sex modulates cognitive ToM remains unknown [17–19]. One possible explanation for this difference is that female brains are less lateralized than male brains [20], which allows for greater communication between the two cerebral hemispheres and, therefore, better integration between emotional-intuitive and cognitive-analytical processing modes [21]. A complementary explanation comes from the different gender roles that men and women have played throughout evolution. From this perspective, sex differences in empathic behaviors could also stem from the greater prosocial and caregiving roles that women typically adopt in most cultures [17,18].

In patients with SCH, sex differences have been observed in several of its clinical features. Compared to women, men tend to show a higher incidence of the disorder, an earlier age of onset and a more severe course of the disease [22]. In patients with BD, these differences are much more diffuse [23]. However, some data suggest that manic episodes are more frequent in men and depressive symptoms in women [24].

Deficits in emotion recognition and ToM are a well-established finding in BD [25,26] and SCH [27,28]. One of the most salient issues among studies comparing the two disorders is the question of whether these deficits are of equal magnitude [29–31]. In general, studies agree that BD patients tend to perform intermediate between SCH patients and healthy individuals [32–46]. However, results are not always concordant [8,47–49], possibly due to methodological differences and shortcomings such as small sample size ($n < 20$ [8,32,34,35,41,46,47] or $n < 30$ [39,42,44,50] in at least one subgroup of the study), the mix of clinically stable and acute patients [32–35,43,48], and the use of different instruments to assess social cognition [51], in particular cognitive ToM.

In this regard, it should be noted that cognitive ToM is not a unitary domain. In fact, it encompasses different sub-processes [52–54], including *first-order* skills (what I think another person thinks or believes), *second-order* skills (what I think another person thinks about what a third party thinks or believes) and other higher order skills (e.g., understanding metaphors, irony, or sarcasm). To date, most studies comparing the two disorders have focused on analyzing higher order ToM [36,41–43,45,48]. All but two of these studies show that BD patients tend to perform better than SCH patients [42,48]. However, the results for first- and second order ToM are contradictory. While some studies found better performance in BD patients than in SCH patients [37,40], at least on second-order skills [32], others found no difference [46,47].

In patients with BD, little is known about the effect of sex on emotion recognition and ToM. To date, only one meta-analysis [25] and another more recent study [12] have specifically explored the effect of sex on emotion recognition, providing conflicting results, while no study has yet examined the relationship between sex, affective ToM and cognitive ToM. In patients with SCH, one review [55] and one meta-analysis [28] found no effect of sex on social cognition. However, a study not included in these publications and two others published shortly thereafter show that women perform better than men in emotion recognition [56,57] and affective ToM [58]. The overrepresentation of male patients in some cohorts [9,12,50,57,59] is a recurrent limitation in the literature [55] that could compromise the generalizability of current knowledge to female patients. The use of a composite variable including measures of emotion recognition, affective ToM, and cognitive ToM in a single index may also be a limitation [42,59], as it does not allow testing whether sex differences in social cognition are domain- or construct-specific.

It has recently been speculated that the advantage of healthy women in emotion recognition and affective ToM may be maintained in women with SCH [56,58,60], and that this may be related to their better clinical outcomes compared to men with SCH [58,61]. However, this contrasts with two meta-analyses in patients with BD and SCH that found that the effect of disease outweighs the effect of sex on emotion recognition [25,28]. Several neuroimaging studies indicate that emotion recognition and ToM share a common neural substrate [1,16]. Therefore, it is possible that the advantage of healthy women in affective ToM is not maintained in these disorders. However, this hypothesis has not yet been tested, at least in BD patients.

In this study, we tried to overcome some of the limitations of previous research by including only clinically stable patients in a male:female ratio of 1:1, using a comprehensive battery with tests of emotion recognition, affective ToM, and first- and second-order cognitive ToM, and by analyzing the emotional, affective, and cognitive aspects of social cognition separately. Our hypotheses were that BD patients will perform intermediate between healthy subjects and SCH patients, that the advantage of healthy women in emotion recognition and affective ToM will be lost in BD and SCH patients, and that clinical variables will modulate their performance. Our aim was threefold: first, to compare emotion recognition, affective ToM, and first- and second-order cognitive ToM in BD, SCH and healthy subjects; second, to examine sex-related differences in emotion recognition, affective ToM, and first- and second-order cognitive ToM in each of the three groups; and third, to explore the modulatory effect of clinical variables on these sub-domains of social cognition.

2. Material and methods

2.1. Participants and procedure

Sixty patients with BD (30 men, 30 women) and sixty patients with SCH (30 men, 30 women) participated in this cross-sectional study. They were recruited at the outpatient mental health clinic of the Parc Taulí University Hospital in Sabadell, Catalonia (Spain), between 2016 and 2019. To be enrolled, patients had to be clinically stable, which was defined as: having been on follow-up treatment for the past 3 months, not having suffered any exacerbation of symptoms during that period, and not having changed psychotropic drug regimen during the past month (including antipsychotics and mood stabilizers/anticonvulsants).

Inclusion criteria for patients with BD were: DSM-IV-TR diagnosis of BD type I/II [62], score ≤ 6 on the Young Mania Rating Scale (YMRS), and score ≤ 14 on the Hamilton Depression Rating Scale (HAM—D) [63]. For patients with SCH, inclusion criteria were: DSM-IV-TR diagnosis of schizophrenia/schizoaffective disorder [62], score ≤ 3 on items

P1 (delusions), P2 (conceptual disorganization) and P3 (hallucinatory behavior) of the Positive and Negative Syndrome Scale (PANSS) [63], and score ≤ 7 on the Calgary Depression Scale for Schizophrenia (CDSS) [64].

The following were considered exclusion criteria: age outside the 18–64 range, any concomitant Axis I/II disorder, substance abuse/dependence in the past 6 months (excluding nicotine and caffeine), any medical or neurological disorder associated with cognitive impairment (including brain damage), electroconvulsive therapy in the past 12 months, or intelligence quotient (IQ) ≤70.

Complementarily, forty healthy subjects (20 men, 20 women) were recruited, matched by age and years of education with the patients. They were recruited from healthy companions of non-psychiatric patients attending the Parc Taulí University Hospital and from other community sources. Exclusion criteria were the same as for the patients, with the addition that they had no history of any Axis I/II disorder. Individuals with first-degree relatives diagnosed with bipolar disorder type I/II, schizophrenia/ schizoaffective disorder, or autism spectrum disorder were also excluded.

The study was approved by the Institutional Review Board of the Parc Taulí University Hospital (#2017/579) and was conducted in accordance with the latest version of the Declaration of Helsinki. All participants were informed about the characteristics of the study and gave written informed consent prior to enrollment. Inclusion/exclusion criteria were confirmed by reviewing electronic medical records and interviewing all participants using a semi-structured clinical interview based on DSM-IV-TR criteria [62].

2.2. Clinical evaluation

In addition to collecting demographic data such as sex, age and years of education, the clinical evaluation included administration of the YMRS [65] and HAM-D [66] in BD patients and the PANSS [67] and CDSS [68] in SCH patients. In patients with SCH, the CDSS was used instead of the HAM-D because it allows better discrimination of depressive symptoms from negative symptoms [69]. Age of onset of the disorder, duration of illness, total number of hospitalizations, history of psychosis (only in BD patients) and psychotropic drugs were also collected.

2.3. IQ and social cognition assessment

IQ was estimated using the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition [70], as it is highly correlated with general intelligence ($r = 0.80$) [71].

The Pictures of Facial Affect (POFA [72]; Cronbach's alpha = 0.810 [73]) was used to assess emotion recognition. Participants were shown 60 monochromatic photographs of adult male and female faces, each depicting one of the six basic emotions (disgust, sadness, anger, fear, surprise, happiness). All stimuli were presented for 5 s along with a 6-option multiple-choice question and subjects were asked to identify the emotion displayed in each photograph. A higher score means better recognition of the basic emotions of others (range 0–60 points).

The revised version of the Reading the Mind in the Eyes Test (RMET [74]; Cronbach's alpha = 0.735 [75]) was used to assess affective ToM. Participants were shown 36 monochromatic photographs of male and female gazes without a preset time limit. All stimuli were presented along with a 4-option multiple-choice question and subjects were asked to discriminate what the individual in each photograph is thinking or feeling (e.g., playful, comforting, irritated, or bored). A higher score means better decoding of the complex emotions of others (range 0–36 points).

Four false-belief stories were used to assess cognitive ToM skills. The first-order cognitive ToM was measured using the Sally & Anne [52] and The Box of Chocolate [54] stories. The second-order cognitive ToM was measured using The Burglar [54] and The Ice-Cream Van [53] stories. The examiner read each story aloud and participants had to answer two questions. The first (ToM) question concerned the subject's false belief about the situation. The second (control) question was intended to assess the subject's comprehension of the story. Results are presented in percentages of failure vs. non-failure. A higher non-failure score means better reasoning about the thoughts and beliefs of others (range 0–100%).

2.4. Data preprocessing

For the purposes of statical analysis, daily doses of antipsychotic drugs were converted to chlorpromazine equivalents [76], antidepressant drugs to fluoxetine equivalents [77], and benzodiazepine drugs to diazepam equivalents [78].

At the time of evaluation, about one-fifth of patients ($n = 26/120$) had subthreshold depressive symptoms. To analyze the impact of these symptoms on social cognition we created a dichotomous variable [63,64]: “Subthreshold depression” was defined by a HAM-D score of 8–14 or a CDSS score of 4–7, and “No depression” by a HAM-D score of <8 or a CDSS score of <4.

To measure the percentages of failure vs. non-failure in cognitive ToM, we created two dichotomous variables (one for each order of cognitive ToM) [56]. These variables were categorized as 0 (no ToM failure) when the participant correctly answered all ToM and control questions of the two same order false-belief stories, or 1 (ToM failure), when the participant incorrectly answered the ToM questions but correctly answered the control questions of the two same order false-belief stories. No participant failed the control questions of the first-order false-belief stories. However, 5 BD patients (4 men, 1 women), 8 SCH patients (6 men, 2 women) and 1 healthy woman failed the control question(s) of the second-order false-belief stories and were excluded from the corresponding analyses. This strict categorization allowed us to control for the possible confounding effect of neurocognitive deficits (e.g., comprehension difficulties), as only participants who correctly answered the control questions were analyzed.

2.5. Statistical analysis

All analyses were performed using SPSS v.19.0. Statistical significance was set at $p < 0.05$. The normal distribution of data was explored using the Shapiro-Wilk test. Skewness and kurtosis were also checked as indicators of deviation from normality. When necessary, log10 and square root transformations were performed to normalize data distribution.

Group and sex differences in continuous demographic, clinical and cognitive variables were analyzed using parametric (ANOVA, Student's *t*-test) and non-parametric (Kruskal-Wallis *H*, Mann-Whitney *U*) tests, as appropriate. For categorical clinical and cognitive variables, the Chi-square test (X^2) was used. To control for possible type I errors, unplanned post hoc analyses (for group differences) and planned multiple comparison tests (for sex differences) were corrected with the Bonferroni method. Effect sizes (Cohen's *d* or Cramer's *V*) are reported for all significant outcomes.

The impact of clinical variables on patients' social cognitive performance was analyzed using a series of bivariate/binomial regressions, as appropriate. Age and estimated IQ were also included in these analyses because of their clinical relevance to cognitive performance [9,56]. Each independent variable that reached statistical significance in these screening analyses was included as a possible factor in their corresponding multiple linear/logistic regression model. 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, multiple collinearity diagnostics were performed. A final model was constructed for each sub-domain of social cognition assessed that included all variables that independently influenced the test score.

Table 1
Demographic data and estimated IQ of the total sample ($n = 160$).

Mean (SD) are reported									
	Patients with BD ($n = 60$)		Patients with SCH ($n = 60$)		Healthy subjects ($n = 40$)		Statistics (Kruskal-Wallis H test)		
	1, Men	2, Women	3, Men	4, Women	5, Men	6, Women	H	p	Post hoc *tests*
n	30	30	30	30	20	20			
Age, *years*	47.5 (8.3)	46.9 (9.2)	44.8 (8.7)	45.1 (8.8)	46.1 (11.2)	45.6 (9.9)	2.619	0.758	
Education, *years*	11.7 (3.1)	11.4 (2.5)	11.1 (2.3)	10.9 (3.1)	12.4 (2.7)	11.3 (3.0)	4.367	0.498	
Estimated IQ***	99.2 (7.1)	98.5 (7.4)	87.7 (9.6)	85.4 (9.7)	100.8 (7.8)	99.5 (7.8)	52.340	<0.001	3, 4 < 1, 2, 5, 6

Note: Estimated IQ is presented in standard scores, which have a mean of 100 and a SD of ±15. *Abbreviations:* IQ, Intelligence quotient; BD, Bipolar disorder; SCH, Schizophrenia/Schizoaffective disorder.
*** $p < 0.001$.

3. Results

3.1. Demographic data and estimated IQ

Table 1 summarizes the demographic data and estimated IQ of the total sample. The groups did not differ in age ($p = 0.420$) or years of education ($p = 0.307$). However, they differed in estimated IQ ($H = 51.495$, $p < 0.001$, $d = 1.796$). Post hoc analysis showed that SCH patients had a lower estimated IQ than BD patients ($U = 606.5$, $p < 0.001$, $d = 1.819$) and healthy subjects ($U = 375.5$, $p < 0.001$, $d = 1.800$), while there were no significant differences between BD patients and healthy subjects ($U = 1.090$, $p = 0.431$).

3.2. Clinical variables

Table 2 summarizes the clinical characteristics of the patient groups. Patients with BD had an earlier age of onset ($d = 0.596$) and a longer duration of illness ($d = 1.377$) than patients with SCH. In contrast, SCH patients received higher doses of chlorpromazine equivalents ($d = 7.012$).

Most patients (78.3%) were free of subthreshold depressive symptoms at the time of evaluation (HAM—D: 3.8 ± 2.2; CDSS: 1.3 ± 1.3). However, 13 patients with BD (6 men, 7 women) and 13 patients with SCH (6 men, 7 women) suffered from subthreshold depression (HAM—D: 9.2 ± 1.8; CDSS: 4.2 ± 0.4).

In the BD group, women had more pronounced depressive symptoms

Table 2
Clinical characteristics of the patient groups ($n = 120$).

Mean (SD) are reported unless otherwise specified				
	Patients with BD ($n = 60$)	Patients with SCH ($n = 60$)	Statistics	
			$t/U/X^2$	p
Diagnostic subtype, *n*				
Type I/II	46/14			
Schizophrenia/Schizoaffective disorder		40/20		
Symptom rating scales				
YMRS Total score	1.0 (1.5)			
HAM-D Total score	5.0 (3.1)			
PANSS Total score		53.8 (12.6)		
Positive scale		9.9 (3.1)		
Negative scale		17.4 (5.7)		
General scale		26.5 (6.0)		
CDSS Total score		2.0 (1.7)		
Course of the disease				
Age of onset, *years**	28.3 (11.1)	32.1 (9.2)	2.286[a]	0.024
Duration of illness, *years****	19.6 (11.5)	10.7 (9.4)	980.0[b]	<0.001
Number of hospitalizations	1.7 (2.0)	2.1 (2.6)	1608.0[b]	0.296
History of psychosis, *n (%)*	34 (56.7)			
Type of psychotropic drugs, *n (%)*				
Antipsychotics (AP)***	0 (0.0)	18 (30.0)	21.176[c]	<0.001
Mood stabilizers/Anticonvulsants	3 (5.0)	0 (0.0)	3.077[c]	0.079
AP + Mood stabilizers/Anticonvulsants	13 (21.7)	6 (10.0)	3.064[c]	0.080
Other combinations (including AD and BZD)	44 (73.3)	36 (60.0)	2.400[c]	0.121
Doses of psychotropic drugs (milligrams/day)				
Chlorpromazine equivalents ($n = 109$)***	252.5 (293.9)	510.8 (382.8)	4.836[a]	<0.001
Fluoxetine equivalents ($n = 55$)	37.0 (19.7)	42.1 (29.4)	0.461[a]	0.647
Diazepam equivalents ($n = 58$)	24.0 (30.8)	19.6 (11.4)	−0.315[a]	0.754

Abbreviations: BD, Bipolar disorder; SCH, Schizophrenia/Schizoaffective disorder; 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.
[a] Student's *t*-test.
[b] Mann-Whitney *U* test.
[c] Chi-square test (X^2).
* $p < 0.05$.
*** $p < 0.001$.

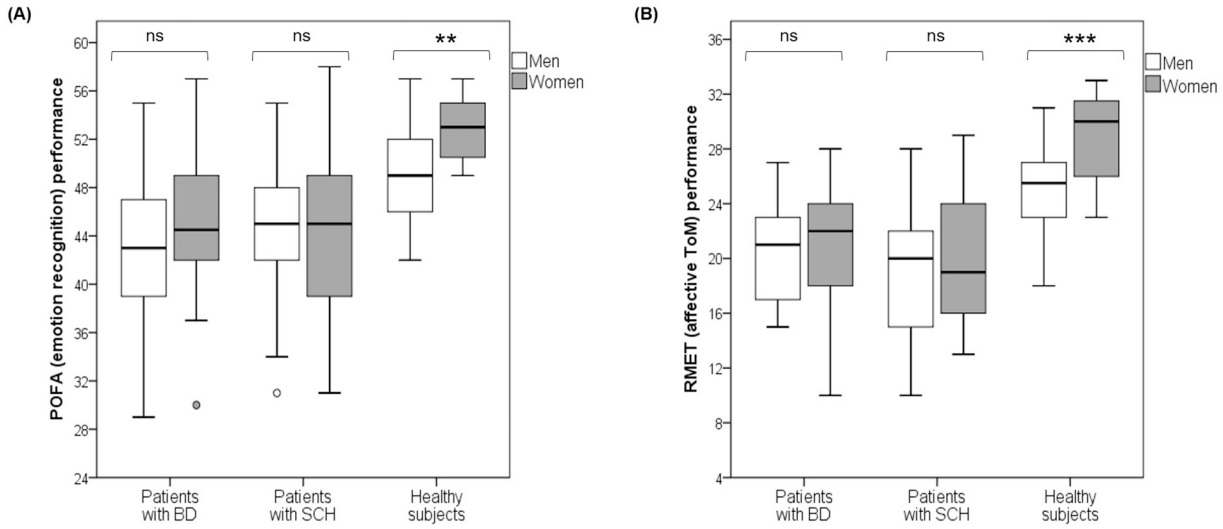

Fig. 1. Sex differences in the POFA (emotion recognition) and RMET (affective ToM) tasks in BD, SCH and healthy subjects. *Note:* Box plots showing the median (bold line), first and third quartiles (middle lines between the bold line and the whiskers), and the minimum and maximum values (whiskers) of the POFA and RMET tasks separated by group and sex. *Abbreviations:* POFA, Pictures of Facial Affect; RMET, Reading the Mind in the Eyes Test; ToM, Theory of Mind; BD, Bipolar disorder; SCH, Schizophrenia/Schizoaffective disorder; ns, not significant. *(A) POFA (emotion recognition) performance.* BD men vs. BD women: 43.5 ± 5.9 vs. 44.9 ± 5.7 ($t_{(58)} = -0.936$, $p = 0.353$); SCH men vs. SCH women: 44.8 ± 5.8 vs. 43.9 ± 6.4 ($t_{(58)} = 0.529$, $p = 0.599$); Healthy men vs. Healthy women: 49.4 ± 4.2 vs. 52.9 ± 2.7 ($t_{(32.1)} = -3.078$, $p = 0.004$). *(B) RMET (affective ToM) performance.* BD men vs. BD women: 20.8 ± 4.0 vs. 21.1 ± 4.4 ($t_{(58)} = -0.276$, $p = 0.783$); SCH men vs. SCH women: 19.4 ± 4.8 vs. 20.1 ± 4.4 ($t_{(58)} = -0.562$, $p = 0.576$); Healthy men vs. Healthy women: 24.9 ± 3.4 vs. 28.9 ± 3.1 ($t_{(38)} = -3.820$, $p < 0.001$). *Statistics:* ** $p < 0.01$; *** $p < 0.001$.

than men (5.7 ± 2.8 vs. 4.2 ± 3.3; $U = 307.5$, $p = 0.034$, $d = 0.429$), but men had suffered more manic episodes than women (2.5 ± 2.4 vs. 1.0 ± 1.2; $U = 273.0$, $p = 0.007$, $d = 0.559$). No other sex-related differences were found.

3.3. Group and sex differences in social cognition

The mean POFA (emotion recognition) score was 44.2 ± 5.8 in BD patients, 44.4 ± 6.1 in SCH patients and 51.1 ± 3.9 in healthy subjects ($F_{(2,157)} = 23.431$, $p < 0.001$, $d = 1.284$). Post hoc analysis showed that healthy subjects performed better than patients with BD ($p < 0.001$, $d = 1.165$) and SCH ($p < 0.001$, $d = 1.131$), while there were no significant differences between patient groups ($p = 1.000$). Sex differences were only found in healthy subjects, with women performing better than men (Fig. 1, A). The significance of this difference remained even after strict Bonferroni correction ($p = 0.012$, $d = 0.942$).

The mean RMET (affective ToM) score was 21.0 ± 4.2 in BD patients, 19.8 ± 4.6 in SCH patients and 26.9 ± 3.8 in healthy subjects ($F_{(2,157)} = 36.608$, $p < 0.001$, $d = 1.397$). Post hoc analysis showed that healthy subjects performed better than patients with BD ($p < 0.001$, $d = 1.115$) and SCH ($p < 0.001$, $d = 1.342$), while there were no significant differences between patient groups ($p = 0.385$). Again, sex differences were

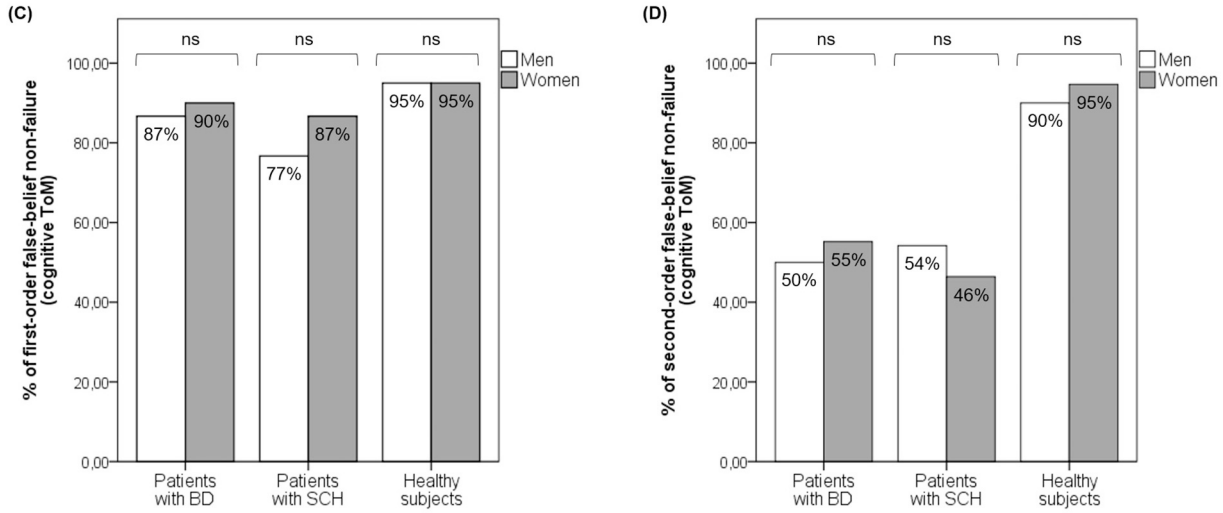

Fig. 2. Sex differences in first- and second-order false-belief tasks (cognitive ToM) in BD, SCH and healthy subjects. *Note:* Bar chart showing the percentage of non-failure in first- and second-order false-belief tasks separated by group and sex. *Abbreviations:* ToM, Theory of Mind; BD, Bipolar disorder; SCH, Schizophrenia/Schizoaffective disorder; ns, not significant. *(C) First-order false-belief non-failure/failure.* BD men vs. BD women: 26/4 vs. 27/3 ($X^2_{(1)} = 0.162$, $p = 0.688$); SCH men vs. SCH women: 23/7 vs. 26/4 ($X^2_{(1)} = 1.002$, $p = 0.317$); Healthy men vs. Healthy women: 19/1 vs. 19/1 ($X^2_{(1)} = 0.000$, $p = 1.000$). *(D) Second-order false-belief non-failure/failure.* BD men vs. women: 13/13 vs. 16/13 ($X^2_{(1)} = 0.147$, $p = 0.701$); SCH men vs. SCH women: 13/11 vs. 13/15 ($X^2_{(1)} = 0.310$, $p = 0.578$); Healthy men vs. Healthy women: 18/2 vs. 18/1 ($X^2_{(1)} = 0.308$, $p = 0.579$). *Statistics:* No significant differences at $p < 0.05$.

only found in healthy subjects, with women performing better than men (Fig. 1, B). The significance of this difference also remained after strict Bonferroni correction ($p = 0.001$, $d = 1.109$).

Additional analyses exploring the effect of group, sex, and group-sex interaction on a variable combining the POFA and RMET tests into a single index can be found in the Supplementary Material. These analyses were repeated adjusting for age and estimated IQ. The results confirm that the two groups of patients perform worse than healthy subjects on emotional and affective aspects of social cognition (Online Resource 1 and 2), that there are no differences between BD and SCH patients (Online Resource 1 and 2), and that the differences between men and women are limited to healthy subjects (Online Resource 2 and 3).

As for first- and second-order cognitive ToM, 88.3% ($n = 53/60$) of BD patients, 81.7% ($n = 49/60$) of SCH patients and 95.0% ($n = 38/40$) of healthy subjects responded correctly to the first-order false-belief task and no significant differences were found between them ($X^2_{(2)} = 3.962$, $p = 0.138$). However, only 52.7% ($n = 29/55$) of BD patients and 50.0% ($n = 26/52$) of SCH patients responded correctly to the second-order false-belief task compared to 92.3% ($n = 36/39$) of healthy subjects ($X^2_{(2)} = 20.454$, $p < 0.001$, $V = 0.374$). Post hoc analysis showed that healthy subjects performed better than patients with BD ($X^2_{(1)} = 16.757$, $p < 0.001$, $V = 0.422$) and SCH ($X^2_{(1)} = 18.372$, $p < 0.001$, $V = 0.449$), while there were no significant differences between patient groups ($X^2_{(1)} = 0.080$, $p = 0.778$). No sex-related differences were found in first- (Fig. 2, C) and second-order false-belief tasks (Fig. 2, D).

To control for the possible confounding effect of BD women's more pronounced depressive symptoms, sex-related analyses were repeated in the BD group, including HAM-D as a covariate. Sex remained non-significant in all sub-domains of social cognition, including the "POFA and RMET variable" ($p \geq 0.165$).

3.4. Impact of age, estimated IQ, and clinical variables on patients' social cognitive performance

Table 3 (A) shows that older age, lower estimated IQ, and younger age of onset were associated with worse POFA performance in bivariate analyses. All other variables had $p \geq 0.05$ and were discarded. In the multiple linear regression model age and estimated IQ, but not age of onset, remained significant factors. The final model included age (B = −0.199, 95% CI = −0.31 to −0.09, $p = 0.001$) and estimated IQ (B = 0.217, 95% CI = 0.12 to 0.31, $p < 0.001$) and explained 18.5% of the variance in emotion recognition (adjusted $R^2 = 0.171$, $F_{(2,117)} = 13.303$, $p < 0.001$).

Table 3 (B) shows that older age, lower estimated IQ, younger age of onset, and higher doses of chlorpromazine and fluoxetine equivalents were associated with worse RMET performance in bivariate analyses. All other variables had $p \geq 0.05$ and were discarded. Again, only age and estimated IQ remained significant factors in the multiple linear regression model. Non-significant variables were extracted from the model in the following order: age of onset ($p = 0.472$), chlorpromazine equivalents ($p = 0.304$) and fluoxetine equivalents ($p = 0.148$). The final model included age (B = −0.153, 95% CI = −0.24 to −0.07, $p < 0.001$) and estimated IQ (B = 0.174, 95% CI = 0.10 to 0.24, $p < 0.001$) and explained 20.9% of the variance in affective ToM (adjusted $R^2 = 0.196$, $F_{(2,117)} = 15.460$, $p < 0.001$).

An additional analysis exploring the impact of age, estimated IQ, and clinical variables on the "POFA and RMET variable" can be found in Online Resource 4 (see Supplementary Material). The results of this analysis are consistent with the data reported so far.

Table 3 (C) shows that lower estimated IQ and subthreshold depression were associated with higher first-order false-belief failure (cognitive ToM) in binomial analyses. All other variables had $p \geq 0.05$ and were discarded. In the multiple logistic regression model, only subthreshold depression remained a significant factor (Nagelkerke R^2 =

Table 3
Impact of age, estimated IQ, and clinical variables on patients' social cognitive performance.

	(A) POFA (emotion recognition)				(B) RMET (affective ToM)			
	Bivariate analyses		Multiple linear regression model		Bivariate analyses		Multiple linear regression model	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Age*	**−0.141 (−0.26 to −0.02)**	**0.022**	**−0.184 (−0.30 to −0.07)**	**0.002**	**−0.106 (−0.20 to −0.02)**	**0.021**	**−0.141 (−0.28 to −0.00)**	**0.049**
Estimated IQ*	**0.180 (0.08 to 0.28)**	**<0.001**	**0.203 (0.11 to 0.30)**	**<0.001**	**0.146 (0.07 to 0.22)**	**<0.001**	**0.165 (0.04 to 0.29)**	**0.011**
Subthreshold depression	−0.428 (−3.03 to 2.17)	0.745			−0.065 (−2.00 to 1.87)	0.947		
Age of onset	**−1.382 (−2.50 to −0.26)**	**0.016**	−0.618 (−1.71 to 0.48)	0.266	**−0.848 (−1.70 to −0.01)**	**0.048**	−0.376 (−1.42 to 0.67)	0.472
Duration of illness	0.008 (−0.09 to 0.10)	0.875			−0.002 (−0.07 to 0.07)	0.958		
Chlorpromazine equivalents	−1.025 (−3.45 to 1.40)	0.404			**−2.537 (−4.29 to −0.78)**	**0.005**	−1.344 (−3.98 to 1.30)	0.310
Fluoxetine equivalents	−4.940 (−10.95 to 1.07)	0.105			**−4.805 (−8.99 to −0.62)**	**0.025**	−2.336 (−6.39 to 1.72)	0.252
Diazepam equivalents	−2.375 (−7.49 to −2.74)	0.357			−0.071 (−3.86 to 3.72)	0.970		

	(C) First-order false-belief failure (cognitive ToM)				(D) Second-order false-belief failure (cognitive ToM)			
	Binomial analyses		Multiple logistic regression model		Binomial analyses		Multiple logistic regression model	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.064 (1.00 to 1.13)	0.051			1.023 (0.98 to 1.07)	0.304		
Estimated IQ	**0.948 (0.90 to 1.00)**	**0.034**	0.949 (0.90 to 1.00)	0.062	**0.953 (0.92 to 0.99)**	**0.016**		
Subthreshold depression*	**6.719 (2.30 to 19.63)**	**<0.001**	**6.398 (2.14 to 19.15)**	**0.001**	2.057 (0.74 to 5.72)	0.167		
Age of onset	1.586 (0.92 to 2.74)	0.099			1.171 (0.79 to 1.75)	0.441		
Duration of illness	1.000 (0.96 to 1.05)	0.987			1.005 (0.97 to 1.04)	0.776		
Chlorpromazine equivalents	1.526 (0.50 to 4.67)	0.459			1.593 (0.67 to 3.77)	0.290		
Fluoxetine equivalents	1.460 (0.07 to 30.68)	0.808			2.243 (0.24 to 21.42)	0.483		
Diazepam equivalents	5.792 (0.58 to 58.22)	0.136			2.000 (0.33 to 12.20)	0.452		

(A), (B) and (C) sample size: $n = 120$, except chlorpromazine equivalents ($n = 109$), fluoxetine equivalents ($n = 55$) and diazepam equivalents ($n = 58$). *(D) sample size:* $n = 107$, except chlorpromazine equivalents ($n = 96$), fluoxetine equivalents ($n = 49$) and diazepam equivalents ($n = 51$). *Abbreviations:* IQ, Intelligence quotient; POFA, Pictures of Facial Affect; RMET, Reading the Mind in the Eyes Test; ToM, Theory of Mind. *Statistics:* Bold = Statistically significant at $p < 0.05$.

* $p < 0.05$ in the multiple linear/logistic regression model.

0.168, $X^2_{(1)} = 15.733$, $p = 0.001$). Consistent with this result, patients with subthreshold depressive symptoms had a higher failure rate on the first-order false-belief task than patients without subthreshold depressive symptoms (38.5% vs. 8.5%; $X^2_{(1)} = 14.329$, $p < 0.001$, $V = 0.346$). This difference was also significant in the BD (38.5% vs. 4.3%; $X^2_{(1)} = 11.562$, $p = 0.001$, $V = 0.439$) and SCH (38.5% vs. 12.8%; $X^2_{(1)} = 4.491$, $p = 0.034$, $V = 0.274$) groups.

Table 3 (D) shows that lower estimated IQ was associated with higher second-order false-belief failure (cognitive ToM) in binomial analyses (Nagelkerke $R^2 = 0.076$, $X^2_{(1)} = 6.277$, $p = 0.016$). However, the Hosmer-Lemeshow test indicated poor fit of the model ($p = 0.026$). Thus, caution is advised when interpreting this result. All other variables had $p \geq 0.05$ and were discarded, so multiple logistic regression analysis was not performed.

Follow-up analyses in the BD group showed that diagnostic subtype (type I/II) and history of psychosis were not significant factors for social cognition performance, including the "POFA and RMET" variable ($p \geq 0.132$). In the SCH group, diagnostic subtype (schizophrenia/schizoaffective disorder) and residual negative symptoms (measured by PANSS Negative) were also not significant factors ($p \geq 0.275$).

4. Discussion

This is the first study to compare emotion recognition, affective ToM, and first- and second-order cognitive ToM in a sample of BD patients, SCH patients, and healthy subjects from a sex-related perspective. Our results show that patients with BD and SCH performed worse than healthy subjects in all sub-domains of social cognition assessed, except for first-order cognitive ToM, which remained preserved in up to 85.0% of cases. However, no differences were found between the two disorders. Instead, patients' deficits were related to older age, lower estimated IQ and/or subthreshold depression. Our results also show that healthy females had a marked advantage in emotion recognition and affective ToM tasks compared to healthy males, but that this difference was not evident in the patient groups.

Looking at sex differences in more detail, it is striking that healthy females showed better emotion recognition and affective ToM skills than healthy males, but performed just as poorly as their male counterparts when diagnosed with BD or SCH. Similar results have been reported in two recent cross-sectional studies in BD patients [59], different psychotic disorders and healthy subjects [57], suggesting that female patients may not retain the advantage in emotion recognition observed in healthy females. Along these lines, a review [55] and two meta-analyses in BD [25] and SCH [28] found that the effect of disease outweighs the effect of sex on this ability and that sex differences in emotion recognition remain isolated in healthy individuals. Our results add to the existing literature that the loss of healthy women's advantage in patients with BD and SCH might also involve affective ToM skills (the ability to decode others' complex emotions). However, other cross-sectional studies using assessment tools similar, although not identical, to those in our study have shown opposite results [12,50,58,60,61]. Therefore, the present findings should be confirmed in future studies with larger samples.

To provide an explanation why the advantage of healthy females in emotion recognition and affective ToM might be lost in BD and SCH patients, we turned to several neuroimaging studies. So far, there is agreement that ToM depends on an intact prefrontal cortex and that, while cognitive ToM is impaired by extensive prefrontal lesions, affective ToM is impaired by localized damage to the ventromedial prefrontal cortex [16], which, in turn, shows broad connections with other areas involved in emotion recognition such as the amygdala [1]. There is evidence that the orbitofrontal cortex to amygdala ratio may be greater in healthy females than in healthy males and that this may be related to the sex differences found in social cognition [79]. However, it has recently been found that this sexually dimorphic difference may be altered in patients with SCH [80]. Beyond these studies, the influence of sex on the neural substrate of social cognition has been little studied [81], especially in patients with BD. Therefore, these ideas point only to hypothesis generation.

The two groups of patients had deficits in emotion recognition, affective ToM and second-order cognitive ToM, but not in first-order cognitive ToM. This result is consistent with previous data indicating that social cognition is altered in BD [5,12,26], while confirming that this deficit is a core feature of SCH [4,6,27]. However, the mental workload required to successfully elaborate a first-order false-belief is lower than that required for a second-order false-belief [52–54]. Therefore, it is possible that first-order cognitive ToM is more resistant to social brain changes than second-order cognitive ToM. Consistent with this idea and with other research in BD [32,37,40,46,47] and SCH [32,37,46,56], first-order cognitive skills were not impaired in the patient groups of our study. Furthermore, we observed that no participant responded correctly to the second-order false-belief task if they had failed the first-order false-belief task, which, in turn, is compatible with a hierarchical relationship between the different sub-domains of social cognition already discussed in previous studies [1,56].

Unlike other research in which BD patients had similar but less severe social cognitive deficits than SCH patients [32–46], we found that the two disorders were equally impaired in both the ability to recognize others' basic emotions and the ability to identify others' cognitive and affective mental states [8,47–49]. This suggests that, at least in these sub-domains of social cognition, the severity of impairment might be comparable between them. In view of this finding, one might speculate that the lack of gradation in the severity of these deficits could be related to between-group differences in disease course or psychotropic drugs. However, in the final regression models, none proved significant for performance in social cognition. Indeed, there is evidence that deficits in emotion recognition and ToM show little or no relationship to these variables in clinically stable patients [12,36,44,50,58,60,61].

In contrast, older age and lower estimated IQ were associated with more severe deficits in specifics aspects of social cognition. Whereas age influenced emotion recognition and affective ToM, estimated IQ was related to emotion recognition, affective ToM, and (possibly) second-order cognitive ToM, but not to first-order cognitive ToM. On one hand, this is consistent with the lower cognitive workload required by this task compared to the other three. On the other hand, it should be kept in mind that IQ is one of the proxy measures of cognitive reserve (the brain's resistance to pathological changes). From this perspective, our finding could also indicate a possible protective effect of this variable, as discussed in a previous study [82].

Finally, we observed that first-order cognitive ToM was only determined by the presence of mild depressive symptoms, but not by the severity of residual negative symptoms or by any other clinical or demographic variable. More specifically, patients suffering from subthreshold depression were up to 6 times more likely to have impaired first-order skills than non-depressed individuals. Therefore, given that this sub-process of cognitive ToM remained preserved in up to 85.0% of cases, this finding is of notable clinical interest because it points to an increased risk of severe ToM deficits in this sub-group of individuals. Similar results have been found in a previous study [11].

This latter finding highlights that, along with impaired emotion recognition, affective ToM, and second-order cognitive ToM in BD and SCH patients, the presence of subthreshold depressive symptoms is likely to disrupt normal first-order cognitive ToM functioning [10,83]. Difficulties in recognizing emotions and understanding the thoughts, beliefs and feelings of others have real-life consequences, such as problems in social relationships due to misinterpretation of the true intentions of others. In addition, a person who is not perceived as socially competent will not be a partner with whom one wants to interact, which could promote social distancing or even isolation [2,3]. Thus, it is conceivable that BD and SCH patients with subthreshold depressive symptoms will be less likely to participate adequately in social situations than their non-depressed counterparts, at least in part because of their

higher failure rate in first-order cognitive ToM skills (38.5% vs. 8.5%). Consistent with this hypothesis, it has been found that the severity of depressive symptoms modulates the relationship between social cognition and social functioning [83].

Finally, our results point to the need for a systematic and regular assessment of both social cognition and subthreshold depression in clinically stable outpatients with BD and SCH, as this will contribute to a more accurate determination of their cognitive deficit profile and to the identification of therapeutic targets aimed at improving their social functioning. According to our results, existing cognitive rehabilitations programs would be useful for both BD and SCH patients, as well as for men and women, since they all showed similar performance in emotion recognition and ToM. However, in patients with subthreshold depressive symptoms, additional effort should be made to train first-order cognitive ToM skills.

When interpreting the results of this study, the following limitations should be considered. First, the cross-sectional design, which does not allow any causal inference between patients' social cognitive deficits and their associated factors. Second, the inclusion of patients with BD type II and schizoaffective disorder, which could help explain the lack of differences in emotion recognition and ToM between patient groups, as better cognitive outcomes have occasionally been found in these clinical populations than in those with BD type I and schizophrenia [15,47]. However, diagnostic subtype was not a significant factor for performance on emotion recognition and ToM in the regression analyses. Therefore, we do not expect this variable to have confounded the results. Third, the relatively small sample size, especially when groups are divided by sex, which limits our ability to draw definitive conclusions about whether sex differences in emotion recognition and affective ToM in healthy individuals are lost in BD and SCH. In contrast, our results are strengthened by careful matching between the clinical samples and with the healthy subjects. Fourth, our study included patients who did not necessarily meet criteria for full depression remission or who had residual negative symptoms. Although this could be considered a methodological limitation, it allows the data to be generalized to most patients with BD and SCH that healthcare professionals treat in their daily clinical practice. Finally, we did not include any tests of social functioning. The relationship between social cognition and social functioning has already been described extensively in previous studies [2,3].

5. Conclusions

The following conclusions can be drawn. First, in healthy subjects sex only influenced affective ToM, but not cognitive ToM, thus confirming that the two ToM processes are somehow independent. Second, the advantage of healthy women in emotion recognition and affective ToM was not maintained in BD and SCH patients, so that disease, not sex, would be the main factor related to the deficit in social cognition. Finally, while replicating previous findings that BD and SCH patients are characterized by mild to severe impairments in social cognition, we found that emotion recognition, affective ToM and first- and second-order cognitive ToM represent at least four sub-domains in which the level of impairment may be comparable between the two disorders. It may be that SCH patients only show more severe deficits than BD patients in the more complex and sophisticated aspects of social cognition, so future studies are encouraged to use more demanding tests when comparing the two disorders.

Contributors

MJ and NC designed the study and wrote the protocol. CM, JMC, JC and AJ recruited the patients and conducted the clinical evaluation. GNV, MVG, MSB and SFG recruited the healthy subjects and conducted the IQ and social cognition assessment. GNV and NC run the statistical analysis. GNV drafted the first version of the manuscript. XG, DP, GL and EV critically reviewed the article for important intellectual content. All authors contributed to data interpretation, approved the final version for publication, and participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Research data

The data that support the findings of this study are available from the corresponding authors upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Declaration of Competing Interest

The authors declare no conflict of interest in relation to the publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2021.152258.

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