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Meta-analysis

Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach

Samamé C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach.

Objective: Deficits in social cognition have been reported in euthymic subjects with bipolar disorder (BD). However, some studies have failed to find differences favoring controls. As most investigations have been conducted with small samples, they have not had sufficient power to detect statistically significant differences. Furthermore, studies communicating positive results have scarcely attempted to estimate effect sizes for patient–control differences. The aim of this study was to summarize the findings of reports on social cognition in patients with euthymic BD and to combine their data to identify possible deficits and quantify their magnitude.
Method: Systematic literature review and meta-analysis.
Results: Impairments of moderate magnitude ($0.5 < d < 0.8$) were noted across mentalizing skills, whereas small but significant effect sizes ($d < 0.5$) were observed for facial emotion recognition. No patient–control differences were found for decision-making.
Conclusion: Meta-analytic findings provide evidence for emotion processing and theory of mind deficits in remitted bipolar patients. However, it is not yet clear whether these areas of impairment are related to neurocognitive dysfunctions or to medication effects. The results are discussed with regard to targets for future neuropsychological research on BDs.

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Key words: Bipolar disorder; cognitive functioning; social cognition; euthymia; meta-analysis

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Summations

- Deficits in theory of mind and emotion processing occur in patients with euthymic BD, whereas decision-making appears to be preserved.
- Moderate effect sizes were noted for mentalizing skills, while differences of small magnitude were found for the recognition of facial affect expressions.

Considerations

- These meta-analytic findings should be interpreted cautiously on account of the modest number of studies included, the heterogeneity observed for effect size distributions, and the paucity of well-established instruments for the assessment of social-cognitive domains.
- Only a small number of studies reported data on potential moderators of cognitive impairment in euthymic patients, such as medication status and residual symptoms.

Introduction

Bipolar disorders (BDs) comprise a heterogeneous group of chronic and recurrent illnesses that produce a strong impact on social and vocational functioning in about two-thirds of those affected (1, 2). Growing evidence has revealed that patients with BD exhibit prominent neurocognitive dysfunc-

tions even during remission (3–6). These deficits are inversely associated with psychosocial adjustment (7–10) and have been acknowledged as powerful predictors of long-term functional outcome (11–14). Similar, although milder, impairments are present in unaffected first-degree relatives of patients with BD (15, 16), thus indicating that defective neurocognitive performance is an enduring component of the neuropsychopathology of the illness rather than being secondary to mood state (17–20) or pharmacological treatment (21–25).

Despite the robust body of work on neuropsychological aspects of BD, research on social cognition is still scant. Social cognition is a multidimensional psychological domain that involves a complex set of processes that enable adaptive social interaction, such as the representation of internal somatic states, knowledge about the self, perception of others, and interpersonal motivations (26). Investigations have focused mainly on three central processes within this construct, namely theory of mind (ToM), emotion processing, and affective decision-making. Theory of mind, also referred to as mentalizing or mind-reading, is the cognitive ability to attribute mental states, such as beliefs, desires, and intents to oneself and others (27). Several types of instruments, with varying levels of complexity, have been used to assess this broad construct in clinical samples. Emotion processing, another central aspect of social cognition, encompasses the capability to identify and discriminate 'basic emotions', which are thought to be innate and have universally recognizable facial expressions (28). Most facial emotion recognition tasks require subjects to either match (matching paradigms) or name (labeling paradigms) pictures of posed facial expressions according to the emotions displayed, including happiness, sadness, anger, disgust, fear, and surprise. Finally, as demonstrated by studies on frontotemporal dementia (29, 30), affective decision-making is a key aspect of prefrontal function that is necessary for an appropriate social behaviour and implies weighing up choices associated with variable degrees of reward and punishment. Different paradigms intending to simulate real-life decision-making processes have been developed and require subjects to weigh short-term gains against potential long-term losses.

Daily clinical work shows that remitted BD patients are very heterogeneous with respect to their social competence. While some patients maintain a high level of social and occupational functioning throughout the course of the illness, a significant amount of subjects suffering from BD exhibit persistent disruptions in social and vocational competence that persist even during periods of symptomatic recovery (31, 32). Recent investigations have reported dysfunctions in facial emotion recognition (8, 33, 34), theory of mind (34–39), and affective decision-making (40) as well as spared social-cognitive abilities in euthymic bipolar patients (41–47). These inconsistent findings may be partly explained by heterogeneity within BD but also by several methodological limitations, such as the employment of different measures of social cognition, the inclusion of poorly matched control groups, varying definitions of euthymia, and high probabilities of type II error owing to small sample sizes in most investigations. Furthermore, many of the studies reporting positive results have not calculated effect sizes for patient–control differences. Hence, the social-cognitive profile of euthymic BD remains unclear, and to date, there are no meta-analytic studies summarizing the findings yielded by empirical work in this area of neuropsychological research.

The traditional concept of manic-depressive illness assumed that affected individuals did not display cognitive decline outside acute episodes (48), distinguishing this entity mainly from schizophrenia. At present, although research findings have refuted this notion, we still accept that once recovered, some patients can achieve full integration into social and professional competence, including the possibility of occupying positions in which social judgment and strategic decision-making are essential tools. Consequently, a better comprehension of social cognition during euthymia has critical importance, not only on account of these clinical implications but because it will finally aid in the broadening of the current knowledge on the neural underpinnings and the etiology of BD.

Aims of the study

The main aims of this review were to synthesize the evidence from studies exploring social cognition in euthymic adults with bipolar disorder and, when possible, meta-analyze their neuropsychological findings to identify possible deficits. An additional goal was to examine the effect of potential moderator variables on the social-cognitive performance of subjects affected by bipolar disorder.

Material and methods

Search strategy and study selection criteria

A literature search was conducted using electronic databases PubMed, ScienceDirect, EBSCO, and

Wiley-Blackwell, covering the period between January 1990 and June 2011, using the following keywords: *bipolar disorder, cognitive functioning, neuropsychology, social cognition, mindreading, theory of mind, mentalising/*mentalizing decision making, reward processing, emotion recognition, affect recognition, and *emotion processing*. The reference lists of review articles on cognitive aspects of BD and the studies identified for inclusion were also crosschecked for additional relevant reports.

The initial search strategy aimed to identify all the empirical literature exploring social cognition in euthymic adults with BD. The results of studies on each domain within social cognition (theory of mind, emotion processing, and decision-making) were then summarized. Reports included in the meta-analysis were selected from the initial pool if they met the following criteria: i) Included an asymptomatic adult (aged between 18 and 65) bipolar patient group diagnosed with BD (I-II-NOS) according to DSM IV or similar criteria. ii) Euthymia was defined on the basis of concurrent depression/mania scores on mood rating scales. iii) Included a healthy control group. iv) There were at least ten subjects in each of the patient and healthy comparison groups. v) Investigated social-cognitive domains. vi) Provided data to estimate patient–control effect size differences.

Furthermore, to conduct meta-analyses, we considered a minimum of three studies reporting the performance on tasks assessing the same aspect of social cognition. If there were studies with overlapping content based on the same patient sample, we only considered the data from the study with the largest sample.

Meta-analytical procedure

Meta-analyses were performed using Comprehensive Meta-Analysis software version 2.0 (49). The effect size for each social-cognitive measure was calculated as the mean difference between bipolar patients and healthy controls divided by the pooled standard deviation (*d*). Hedge's formula was applied to correct for upwardly biased estimation of the effect size in small samples. When means and standard deviations were not reported, *d* was calculated from *t* values. In only one study (41) in which no between-group differences were reported, in the absence of further statistics, an effect size of zero was conservatively assumed. Effect sizes were weighted using the inverse variance method. Whenever patients with BD performed poorer than controls, we reported between-group differences by positive effect sizes. If more than one (sub)task was used to assess social-cognitive domains and more than one effect size was thus reported, a pooled effect size was calculated. Whenever means and standard deviations of more than one group with euthymic BD were given, the mean values and standard deviations were combined. Measures with dichotomous outcomes were excluded. The homogeneity of the resulting mean weighted effect sizes for each variable was tested using the Q-statistic and I^2 index. Based on the small sample sizes and the presence of heterogeneity in many of the analyses, we chose a random effects model, which assumes that the true effect size varies from one study to another. Under this model, the studies included in the meta-analysis represent a random sample of the relevant distribution of effects, and the summary measure estimates the mean effect in this distribution (50). Egger's test was used to assess whether there was a tendency for selective publication of positive results. A significance level of $P < 0.05$ was used for the random effects model, homogeneity, and publication bias analyses.

Subgroup analyses were undertaken to explore social cognition in patients meeting stringent criteria of euthymia. Meta-regressions were performed to examine the effects of potential moderator variables (age, duration of illness, sex ratio, years of education, cognitive flexibility, and usage of antipsychotics, antidepressants and benzodiazepines) on observed between-group differences. A mixed effects model under restricted-information maximum likelihood was employed with a significance level of $P < 0.05$. Sensitivity analyses were conducted to explore the quality of studies and heterogeneity.

Social-cognitive variables

Emotion processing. The most commonly utilized tasks in research on bipolar disorders included the stimuli created by Ekman and Friesen (28), which consist of facial expressions of universally recognized (basic) emotions, including happiness, sadness, anger, disgust, fear, and surprise.

Seven different effect sizes were calculated to analyze emotional processing abilities in patients with BD. The overall accuracy was estimated by combining the effect sizes for studies exploring the ability to evaluate the emotional state of others by means of tasks requiring the recognition of six basic emotions using visual stimuli. The accuracy at recognizing each emotion was also calculated through the combination of studies assessing the recognition of the same affect expression.

Theory of mind. Different types of instruments have been used to assess this broad construct in patients with BD. The most common mentalizing measures are false-belief comprehension tasks, which assess subjects' ability to understand that others can hold beliefs that are different from reality (first-order false belief). In a more complicated version, subjects are required to infer the false belief of one character about the belief of a second character (second-order false belief). Two types of false-belief tasks were included in the current meta-analysis: false-belief stories and false-belief picture sequencing (51–53). *Faux pas* recognition (54) is another well-known measure of mentalizing abilities. This task consists of a series of stories which may or may not contain a social *faux pas* (one of the characters says something that it would be better not to say). After being read each story, subjects are asked whether something inappropriate was said and if so why. Finally, the hinting task (51) is another basic measure of mentalizing abilities included in this quantitative review and requires the inference of other's real intentions behind indirect speech.

Measures of complex mindreading such as Happe's (55) strange stories, the Movie for the Assessment of Social Cognition – MASC – (56) and Eyes tasks based on Baron Cohen et al. (57) were also considered for this meta-analysis. Besides, an advanced task requiring subjects to attribute mental states to animated geometric shapes was included (58). These tasks are sensitive to more subtle ToM deficits, involving the comprehension of complex mental states, irony, sarcasm, and double bluff.

Because of the wide variety of tasks employed in research on social cognition in BD, we attempted to group tasks considered similar in nature or assessing the same ToM aspect. However, owing to the lack of information on the psychometric properties of these instruments, fully objective criteria could not be followed. The results of nine studies exploring ToM abilities by means of different tasks were combined in a total ToM score. Moreover, the effect size for basic mentalizing skills was calculated by combining the findings from six studies that explored first- and second-order ToM, *faux pas*, and hinting comprehension. We also calculated the effect size for complex mindreading by combining seven reports that included reading the mind in the eyes, irony comprehension or third-order ToM tasks. Additionally, we estimated patient–control effect size differences for two individual tasks (second-order false belief and eyes test).

Decision-making. The findings of five studies exploring decision-making in euthymic bipolar patients by means of tasks involving simulated gambling, among which the Iowa gambling task – IGT –(29) was the most commonly utilized, were combined in a total decision-making score. Besides, as the results for the overall performance $[(c + d) - (a + b)]$ on the IGT were documented in three studies, a summary IGT score was calculated.

In summary, the outcome variables included in this study were i) emotion processing: overall accuracy and accuracy on the recognition of each emotion; ii) theory of mind: total ToM score, basic mentalizing, complex mindreading, second-order false belief and eyes test; and iii) decision-making: total decision-making score and total IGT score.

Moderator variables

The empirical literature has proposed a number of variables that may affect social cognition (55, 59–67) and therefore influence patient–control differences. When possible, these variables were coded to evaluate their influence on the effect sizes. Potential moderator variables considered in this work were age, gender ratio, percentage of patients medicated with antipsychotics, antidepressives, and benzodiazepines, years of education, and duration of illness. One difficulty in performing meta-regression analyses was the limited data available for moderator variables. In fact, other variables with a potential influence on effect sizes, such as residual mood symptoms, percentage of patients receiving monotherapy with mood stabilizers, medication dose, IQ, attention, and different components of executive functioning, could not be analyzed because available data were insufficient.

Results

The search strategy identified 65 studies, of which 46 explored emotion recognition/theory of mind and 19 examined decision-making in patients with BD. Only 34 reports included euthymic adult patients (8, 33–47, 68–84). The results are summarized in Table 1. When these articles were examined further, only 22 of them met all the inclusion criteria required for this meta-analysis. Two studies were excluded as they were based on the same sample used in other studies (8, 42). Finally, 20 reports comparing the social-cognitive performance of 650 BD patients with that of 607 healthy controls were included in the current meta-analysis (Table 2).

Table 1. Main studies exploring social cognition in adults with euthymic bipolar disorder

Primary study	Subjects	Criteria of euthymia	Social-cognitive aspect involved	Results
Addington & Addington (68)	40 BD 40 SCH 40 HC Euthymic (n = 39)	?	Facial emotion recognition	BDs performed significantly more poorly than HCs, but not as poorly as SCHs
Rubinsztein et al. (41)	18 BD 18 HC Euthymic (n = 18)	HDRS<8, YMRS<8	DM	Response latency was increased in BD patients compared with HC, although accuracy on the task was not impaired
Clark et al. (42)	30 BD 30 HC Euthymic (n = 30)	HDRS<8, YMRS<8+ clinical judgment	DM	Preserved
Harmer et al. (43)	20 BD 20 HC Euthymic (n = 20)	HDRS≤8, YMRS≤8+ clinical judgment	Facial emotion recognition	Facilitated recognition of disgust
Lembke & Ketter (44)	24 BD 10 HC Euthymic (n = 16)	HDRS<10, YMRS<10	Facial emotion recognition	Impaired (only in mania). Enhanced fear recognition in euthymia (only in BD-II)
Kerr et al. (45)	48 BD 15 HC Euthymic (n = 13)	BDI, BMS. Cut off scores?	1st and 2nd order false belief	Impaired ToM in depression and mania, preserved in euthymia
Inoue et al. (69)	16 BD 34 MDD 50 HC Euthymic (n = 16)	HDRS≤7 (remitted depression)	1st and 2nd order false belief	Impaired ToM ability in BD and MDD
Venn et al. (46)	17 BD 17 HC Euthymic (n = 17)	HDRS<8, YMRS<8	Facial emotion recognition	Preserved
Bora et al. (35)	43 BD 30 HC Euthymic (n = 43)	HDRS<7, YMRS<6	Complex mentalizing and emotion recognition	Impaired
Olley et al. (36)	15 BD 13 HC Euthymic (n = 15)	HDRS<12, YMRS<12	2nd order false belief	Patients performed poorly on tests of verbal ToM but not on non-verbal mentalizing tasks. BDs were slower to initiate response
Bozikas et al. (33)	19 BD 30 HC Euthymic (n = 19)	MADRS≤8, YMRS≤8	Facial emotion recognition	Impairment in patients with BD was restricted to the matching of facial emotional expressions despite their intact perception of facial identity
Christodoulou et al. (70)	25 euthymic BD Without control group	MADRS<11, YMRS<7	DM	Positive correlation between non-planning impulsivity and suboptimal DM
Malhi et al. (71)	10 BD 10 HC Euthymic (n = 10)	HDRS≤6, YMRS≤6	Facial emotion recognition	Patients with BD were equally accurate in identifying facial expressions as HC, but were slower to respond to fear and disgust. BD patients showed increased neural response to fear, while HC responded more to disgust
Vaskinn et al. (63)	21 BD 31 SCH 21HC Euthymic (n = 21)	IDS-C < 30, YMRS<12	Facial emotion recognition	Preserved
Hassel et al. (72)	19 BD 24 HC Euthymic (n = 19)	HDRS<11, YMRS<10	Facial emotion recognition	No significant differences in task performance were found. Abnormal patterns of subcortical limbic and dorsal prefrontal cortical activity in response to emotional faces were observed in BDs
Lahera et al. (37)	75 BD 48 HC Euthymic (n = 75)	HDRS<8, YMRS<8	Complex mindreading	Impaired
Malhi et al. (73)	20 BD 20 HC Euthymic (n = 20)	HDRS≤6, YMRS≤6	Complex mentalizing	Impaired
Martino et al. (8)	50 BD 30 HC Euthymic (n = 50)	HDRS≤8, YMRS≤6	Facial emotion recognition	Impaired recognition of disgust and fear
Pizzagalli et al. (74)	18 BD 25 HC Euthymic (n = 13)	HDRS≤8, YMRS≤6	DM	Reduced and delayed acquisition of response bias toward the most frequently rewarded stimulus
Robinson et al. (75)	15 BD 16 HC Euthymic (n = 15)	HDRS, YMRS. Cut off scores?	Facial emotion recognition	Groups did not differ in terms of accuracy or reaction time for any of the task conditions. BDs showed hyperactivation in inferior prefrontal cortical regions compared with HC
Yechiam et al. (76)	28 BD 25 HC Euthymic (n = 14)	YMRS. Cut off score?	DM	Both euthymic and acute patients had a good performance on the task. Compared with HC, increasingly erratic choices were observed in acute patients
Chandler et al. (77)	20 BD (II-NOS)/20 HC Euthymic (n = 20)	HDRS, YMRS. Cut off scores?	DM	BD subjects and HC made the same proportion of risky choices
Holmes et al. (78)	55 BD 25 HC Euthymic (n = 28)	HDRS<10, YMRS<10	DM	Impaired (only in subjects with a prior history of alcohol abuse or dependence). Severity of mood symptoms was not associated with task performance
Kim et al. (79)	14 BD 14 HC Euthymic (n = 14)	HDRS≤7,YMRS≤5	Facial emotion recognition	Delayed reaction times in emotional conditions compared with controls. Reduced activations in the 'mirror neuron system'
Malloy-Diniz et al. (80)	39 BD 53 HC Euthymic (n = 20)	BDI<11, YMRS<11	DM	Impaired. Negative correlation between the number of suicide attempts and task performance

Table 1. Continued

Primary study	Subjects	Criteria of euthymia	Social-cognitive aspect involved	Results
Shamay-Tsoory et al. (81)	19 BD 20 HC Euthymic (n = 19)	HDRS≤9, YMRS≤7+ self-report + confirmation by the family	Facial emotion recognition, *Faux Pas*, empathy, complex mentalizing	Significant deficits in cognitive empathy and *Faux Pas*, with enhanced affective empathy were observed in BDs. No between group differences were found for basic and complex emotion recognition
Almeida et al. (82)	30 BD 15 MDD 15 HC Euthymic (n = 15)	HDRS. Cut off score?	Facial emotion recognition	No between-group differences in emotion labeling accuracy were observed for remitted BDs. Only depressed BDs exhibited defective task performance and abnormal amygadala activity
Jaracz et al. (83)	30 BD 25 HC Euthymic (n = 30)	HDRS≤8, YMRS≤6	DM	Preserved
Martino et al. (47)	85 BD 34 HC Euthymic (n = 85)	HDRS≤8, YMRS≤6	DM	Preserved. Patients with a history of suicide attempt scored worse than non-suicide attempt patients
Montag et al. (38)	29 BD 29 HC Euthymic (n = 29)	HDRS<14, YMRS<5	Complex emotion recognition and mentalizing	Patients scored significantly lower for 'cognitive' but not for 'emotional' ToM
Surguladze et al. (84)	20 BD 20 FDR 20 HC Euthymic (n = 20)	?	Facial emotion recognition	BDs and FDRs were accurate at identifying emotions. Exaggerated medial prefrontal cortical and subcortical (putamen and amygdala) responses to emotional signals were observed in patients and in their FDRs
Wolf et al. (39)	33 BD 29 HC Euthymic (n = 11)	HDRS<15, YMRS<12	1st, 2nd and 3rd order ToM	Impaired ToM in different phases of illness
Adida et al. (40)	315 BD 150 HC Euthymic (n = 90)	HDRS<8, YMRS<6	DM	Impaired DM was observed in mania, depression, and euthymia, with no significant differences between the three BD groups
Martino et al. (34)	81 BD 34 HC Euthymic (n = 81)	HDRS≤8, YMRS≤6	Facial emotion recognition, *Faux Pas*, complex mindreading	Patients with BD had lower performance than HCs on mindreading tasks, and lower recognition of fear facial expression

BD, patients with bipolar disorder; MDD, patients with major depressive disorder; SCH, patients with schizophrenia; HC, healthy controls; FDR, First-degree relatives; BDI, Beck Depression Inventory; BMS, Bech Mania Scale; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; IDS-C, Inventory of Depressive Symptomatology; ToM, theory of mind; DM, decision-making; ?, not given.

Meta-analytic findings

For emotion processing and decision-making analyses, there were no significant between-group differences for age. In the ToM analysis, significant differences were found for this variable (d = 0.21, CI = 0.43–1.97, P = 0.049, k = 9), although in the small range. No differences were observed in any of the analyses regarding years of education.

The results of this quantitative review revealed impairments of small effect size (d = 0.35) for emotion processing overall accuracy, with relatively homogeneous distribution of effect sizes (Fig. 1; Table 3). Because of the wide variety of criteria utilized to define euthymia, a subgroup analysis was performed including only those studies using a cutoff score of 8 in both Hamilton Depression Rating Scale – HDRS – (85) and Young Mania Rating Scale – YMRS – (86). Four studies included patients fulfilling such criteria (34, 35, 43, 46) and were included in the analysis. The summary measure was identical to that obtained in the former analysis (d = 0.35, CI = 0.09–0.62, P = 0.01), and the hypothesis of homogeneity was not rejected (Q-test P = 0.36 I^2 = 6%).

However, we were not able to find statistically significant differences for any of the six basic emotions (Table 3), which may be due to the fact that not all studies provided information regarding each of the emotions separately, and therefore, a smaller number of studies were included in these analyses. Besides, owing to the high levels of heterogeneity observed in the effect size distributions for fear and disgust, the conclusions of these meta-analyses are compromised.

The three meta-analyses of combined ToM measures demonstrated statistically significant mentalizing impairments in patients with BD. Deficits of medium to large magnitude (d = 0.79) were observed for the total ToM score (Fig. 1; Table 3), in the presence of significant heterogeneity. In a sensitivity analysis, this heterogeneity largely disappeared (before: Q-test P = 0.001, I^2 = 70%; after: Q-test P = 0.74, I^2 = 0%) when excluding two studies (39, 73), although the effect size remained significant and in the medium range (d = 0.53, CI = 0.34–0.72, P < 0.00001). In the presence of homogeneity, identical results were obtained using a fixed effects model. A subgroup analysis of reports including patients fulfilling more stringent criteria

Table 2. Characteristics of the studies included in the meta-analysis

Primary study	Groups	Mean age (SD)	% Male	Matched	Duration of illness	%AD	%BZD	%AP	Social-cognitive variable	ES
Rubinsztein et al. (41)	18 BD 18 HC	42 (2)	?	Age, gender, crystallized IQ, MMSE score	17.3	28	0	?	Decision-making	0.00
Harmer et al. (43)	20 BD 20 HC	37.8 (2.5)	50	Age, years of education, crystallized IQ, performance IQ, socioeconomic status	?	30	0	15	Emotion processing Happiness Sadness Fear Disgust Anger Surprise	−0.11 0.12 0.36 −0.44 −0.65 −0.12 0.10
Kerr et al. (45)	13 BD 15 HC	46.8 (9.35)	47	Crystallized IQ	12.9	8	0	31	1st-order ToM 2nd-order ToM	0.56 −0.34
Venn et al. (46)	17 BD 17 HC	44.4 (3.20)	59	Age, gender, years of education, crystallized IQ	?	35	0	47	Emotion processing Happiness Sadness Fear Disgust Anger Surprise	0.61 0.39 −0.09 0.73 0.05 0.32 0.29
Bora et al. (35)	43 BD 30 HC	38.6 (9.33)	53	Age, gender, years of education	15.1	0	5	14	Emotion processing Hinting Task Eyes Test	0.31 0.67 0.66
Olley et al. (36)	15 BD 13 HC	39.20 (11.83)	47	Age, gender, crystallized IQ, handedness	?	?	?	?	Verbal ToM Non-verbal ToM	0.91 0.20
Bozikas et al. (33)	19 BD 30 HC	39 (11)	42	Age, gender, years of education	13	?	?	?	Emotion processing	1.01
Malhi et al. (71)	10 BD 10 HC	33.5 (8.7)	0	Age, gender, handedness, years of education	12	0	0	0	Recognition of fear Recognition of disgust	−0.16 0.50
Vaskinn et al. (63)	21 BD 31 HC	38.1 (9.3)	52	Gender, years of education, total IQ, crystallized IQ	11.5	24	0	57	Emotion processing	0.08
Lahera et al. (37)	75 BD 48 HC	48.2 (11.7)	39	Age, gender, years of education	20.5	?	?	28	Complex ToM	0.53
Malhi et al. (73)	20 BD 20 HC	35.3 (9.4)	55	Age, gender, handedness, years of education	13.1	0	0	0	Complex ToM Intentionality Appropriateness	 1.77 1.54
Chandler et al. (77)	20 BD 20 HC	19.2 (0.26)	45	Age, IQ	19.2	0	0	0	Decision-making	0.00
Kim et al. (79)	14 BD 14 HC	30.4 (5.9)	57	Age, gender, years of education, IQ	4.3	?	?	43	Recognition of anger Recognition of happiness	0.18 0.28
Shamay-Tsoory et al. (81)	19 BD 20 HC	40.2 (13.9)	53	Age, gender	?	0	0	0	Emotion processing Cognitive *Faux Pas* Affective *Faux Pas* Eyes test	0.03 1.11 0.43 0.47
Jaracz et al. (83)	30 BD 25 HC	40 (12)	50	Age, gender, years of education	?	?	?	?	Decision-making	0.05
Martino et al. (47)	85 BD 34 HC	39.9 (10.5)	32	Age, gender, years of education, crystallized IQ	12	34	48	58	Decision-making	−0.10
Montag et al. (38)	29 BD 29 HC	44 (12.9)	34	Age, gender, crystallized IQ	21	38	7	45	Complex mindreading	0.83
Wolf et al. (39)	11 BD 29 HC	49.7 (16.62)	36	Gender, crystallized IQ	16	27	0	73	ToM sum score ToM sequencing 1st-order ToM question 2nd-order ToM question 3rd-order ToM question	2.30 2.14 1.51 2.05 2.30
Adida et al. (40)	90 BD 150 HC	39.3 (12)	36	Age, gender, IQ	14.6	43	30	24	Decision-making	0.35
Martino et al. (34)	81 BD 34 HC	39.8 (10.3)	35	Age, years of education, crystallized IQ	11.9	36	48	54	*Faux Pas* detection Eyes Test Emotion processing Happiness Sadness Fear Disgust Anger Surprise	0.58 0.15 0.49 0.00 −0.09 0.65 0.57 0.01 0.09

ToM: theory of mind; BD: euthymic patients with bipolar disorder; HC: healthy controls; AD: antidepressive medication; BZD: benzodiazepines; AP: antipsychotic medication; MMSE: Minimental State Examination; ES: effect size: ?: not given.

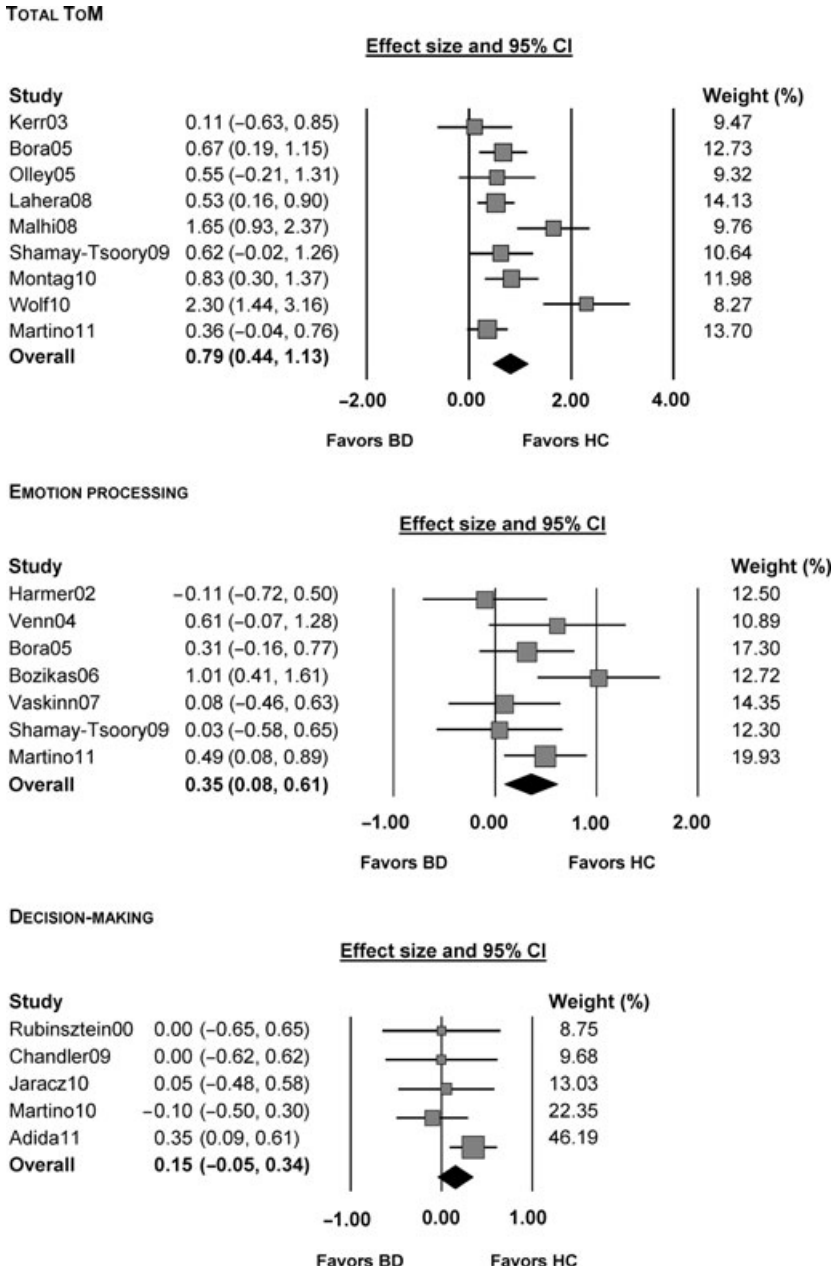

Fig. 1. Forest plots of individual and pooled random effect estimates of the standardized mean differences between bipolar patients and healthy controls for theory of mind (ToM), emotion processing and decision-making total scores.

of euthymia (34, 35, 37, 73) was conducted. The results provided evidence for ToM impairments of moderate to large effect size (d = 0.72, CI = 0.29–1.14, $P < 0.001$) in the presence of high levels of heterogeneity. After excluding the study by Malhi et al. (73), heterogeneity disappeared (before: Q-test $P = 0.02$, $I^2 = 69\%$; after: Q-test $P = 0.62$, $I^2 = 0\%$), and the differences were still significant and in the medium range (d = 0.50, CI = 0.27–0.74, $P < 0.0001$).

For basic ToM and complex ToM, moderate (d = 0.75) and large (d = 0.86) effect sizes were observed, respectively (Fig. 2; Table 3), and the effect sizes were distributed heterogeneously. When adjusting for heterogeneity in the former analysis (before: Q-test $P = 0.02$, $I^2 = 62\%$; after: Q-test $P = 0.73$, $I^2 = 0\%$) by excluding one report (39), the effect sizes remained statistically significant and in the medium range (d = 0.58, CI = 0.33–0.83, $P < 0.0001$). The same result could be obtained using a fixed effects model. In the analysis of complex mindreading, heterogeneity was caused by two studies (39, 73). After leaving these studies out, no significant heterogeneity was observed (before:

Table 3. Mean weighted effect sizes of patient–control differences for social-cognitive domains

Variable	Studies (*k*)	Patients	Controls	ES*	95% CI	*Z*†	*P*	*Q*-test (*P*)‡	Bias (*P*)§
Total ToM	9	306	238	0.79	0.44 to 1.13	4.46	<0.0001	0.001	0.12
Basic ToM	6	182	141	0.75	0.34 to 1.16	3.61	<0.001	0.02	0.51
Complex ToM	7	278	210	0.86	0.42 to 1.30	3.83	<0.001	<0.001	0.02
2nd-Order False Belief	3	39	57	0.74	−0.59 to 2.07	1.09	0.28	0.001	0.20
Eyes test	3	143	84	0.40	0.07 to 0.72	2.38	0.02	0.26	0.63
Emotion processing (total accuracy)	7	220	182	0.35	0.08 to 0.61	2.59	0.01	0.13	0.85
Recognition of happiness	4	132	85	0.13	−0.14 to 0.41	0.96	0.34	0.75	0.12
Recognition of surprise	3	118	71	0.13	−0.16 to 0.43	0.89	0.37	0.87	0.50
Recognition of sadness	3	118	71	0.01	−0.28 to 0.31	0.09	0.93	0.46	0.65
Recognition of anger	4	132	85	0.1	−0.17 to 0.38	0.73	0.46	0.81	0.79
Recognition of fear	4	128	81	0.22	−0.36 to 0.80	0.73	0.46	0.009	0.44
Recognition of disgust	4	128	81	0.15	−0.45 to 0.75	0.48	0.63	0.006	0.43
Total DM score	5	243	247	0.15	−0.05 to 0.34	1.46	0.15	0.37	0.15
IGT	3	205	209	0.14	−0.16 to 0.44	0.92	0.36	0.16	0.42

ToM, theory of mind; DM, decision-making; IGT, Iowa gambling task.
*Effect Size (*d*).
†Test of significance of effect size.
‡Test of homogeneity, based on χ^2 with $k - 1$ degrees of freedom.
§Egger's test of publication bias.

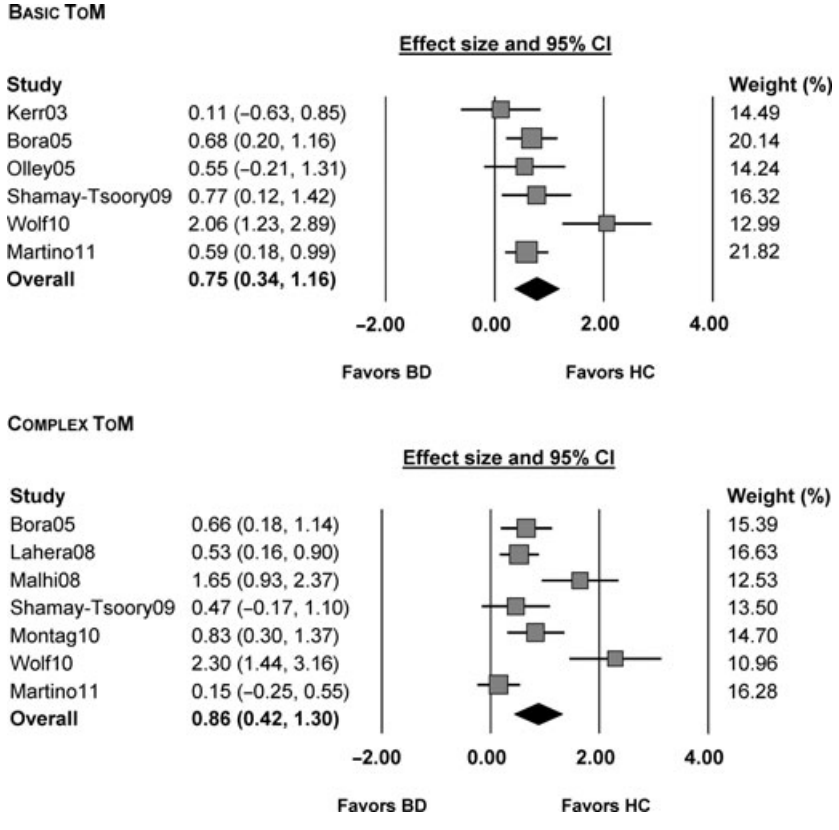

Fig. 2. Forest plots of individual and pooled random effect estimates of the standardized mean differences between bipolar patients and healthy controls for basic and complex theory of mind (ToM).

Q-test $P < 0.001$, $I^2 = 79\%$; after: *Q*-test $P = 0.31$, $I^2 = 17\%$), with significant differences in moderate effect size ($d = 0.5$, CI = 0.27–0.73, $P < 0.0001$). Very similar results could be obtained using a fixed effects model. Evidence of publication bias was observed in the analysis of complex ToM. However, after adjusting for heterogeneity, the evidence of bias disappeared, indicating that the results of Egger's test could be attributable to differences in characteristics of primary studies rather than a tendency to selectively report positive results.

Individual eyes task analysis demonstrated small-to-moderate extent of impairment ($d = 0.4$) with homogeneous effect size distribution (Table 3), in spite of the different stimuli used across studies. In contrast, second-order ToM analysis revealed no significant differences. However, the small number of studies included and the high levels of heterogeneity indicate that the summary measure obtained may not be a valid estimation.

On the other hand, no between-group differences were found for decision-making, neither in the combined tasks analysis nor in the IGT analysis, and the effect sizes distributed homogeneously in both analyses.

Meta-regression analyses revealed that patient–control differences in age and years of education as well as duration of illness and sex ratio were not associated with ToM or emotion recognition performance. Percentages of patients taking benzodiazepines, antidepressants, and antipsychotics were not associated with patient–control effect size differences for social-cognitive domains. Studies with higher percentages of patients taking antipsychotics tended to report larger effect sizes in the emotion processing analysis, but this association failed to reach statistical significance. However, these results are limited by the small number of studies included in the meta-regression.

Discussion

The present study was conducted to compare the social-cognitive performance of euthymic BD patients with that of healthy controls, to identify possible deficits and quantify their magnitude. Three domains within social cognition were considered and meta-analyzed separately, yielding three summary measures: ToM total score, emotion processing, and decision-making. Separate analyses were performed for two different ToM aspects (basic mentalizing and complex mindreading) and for three individual tasks (second-order false belief, eyes task, and Iowa gambling task).

To the best of our knowledge, this is the first study to meta-analyze the findings of different reports on social cognition in patients with euthymic BD. According to Cohen's convention (87), the results showed that impairments occur in BD with medium-to-large effect sizes for total ToM score, large effect sizes for complex mentalizing and medium-to-large effect sizes for basic ToM. When heterogeneity was controlled, patient–control differences remained significant, with all three effect sizes corresponding to the medium range ($0.5 < d < 0.8$). In the presence of high levels of homogeneity, the same summary measures could be obtained using either a fixed or a random effects model, supporting the robustness of these results. Similar results were obtained in a subgroup analysis of studies including patients fulfilling more stringent criteria of euthymia. Among the individual ToM tasks meta-analyzed, eyes task demonstrated small-to-moderate extent of impairment ($d < 0.5$) with relatively homogeneous effect size distribution. Contrarily, second-order ToM analysis revealed no significant differences, and the distribution of effect sizes was highly heterogeneous, which indicates that the justification for an integrated result becomes difficult. Heterogeneity observed for the effect size distribution across ToM analyses was probably due to the fact that very few studies employed identical tasks: there is a significant amount of variation between mentalizing tests in the operationalization of the construct, their complexity (depending on the aspect of ToM involved), the kind of stimuli used (verbal, visual, static, dynamic), and the number of items included, which makes difficult to compare results between studies. In line with this, one of the studies causing heterogeneity (73) employed an advanced mentalizing task that had not been previously used in studies on BD and could probably be a more sensitive instrument to capture impaired mindreading performance. Furthermore, heterogeneity may be also explained by the methodological limitations that are common to investigation into cognitive aspects of BD: varying criteria of euthymia, heterogeneous samples, usage of different medication, among others.

With regard to emotion processing, impairments of small effect size were observed ($d < 0.5$) in the presence of relative homogeneity. The same result was obtained in a subgroup analysis of studies including patients fulfilling stricter criteria of euthymia. Unluckily, we were not able to study the specificity of emotion processing deficits owing to the paucity of information on the recognition of each basic emotion. Finally, the results of this quantitative review indicated that decision-making abilities are preserved in patients with euthymic BD, with a homogeneous effect size distribution for both combined and single task analyses.

One key finding of our study is that not all social-cognitive domains are equally impaired, highlighting the importance of conceptualizing social cognition as a complex set of different processes that not necessarily must be involved and have different neural correlates. The fact that mindreading in the eyes is quite preserved provides evidence for this task being a measure of a different ToM component, probably more linked to affect

processing or empathy. Recent researches proposed that ToM comprises two distinct aspects: mental state decoding (social-perceptual) and mental state reasoning (social-cognitive) (88, 89). The social-perceptual component involves the capability to perceive the mental state of others based on observable information such as facial expressions or gestures. Although this concept is closely associated with the recognition of basic emotions, it also has a ToM component, which may not be necessary for the recognition of facial affect expressions. The social-cognitive component involves the capacity to integrate the contextual and historical information about a person (attitudes, knowledge, and experiences) to understand behaviour. Moreover, there is accumulating evidence revealing that both components of ToM might rely on different social brain networks. While orbitofrontal cortex and temporal cortex activation might be related to the social-perceptual component, the activation of frontal medial cortex may play a critical role in the social-cognitive component (89, 90). Likewise, there is increasing evidence from neuropsychological and neuroimaging studies, indicating that separable neural substrates may exist for the processing of different facial expressions (91–93).

We believe that our findings alone are insufficient to draw firm conclusions about ToM and emotion processing being trait markers of BD. Subthreshold affective symptoms, neurocognitive impairments, and medication are major confounds and could be contributing to social cognition dysfunction. Absolute mood stability is unusual in bipolar patients, and subclinical affective symptoms have a negative influence on neurocognitive functioning (42, 94). In line with this, the study responsible for heterogeneity in the three combined ToM analyses (39), which reported differences of large effect size, was conducted with patients considered as remitted according to a very broad definition of euthymia. Differences of similar magnitude ($d > 0.8$) in second-order false-belief comprehension were found in a recent study including patients who were not in full remission (95). Hence, residual mood symptoms may also be contributing to the heterogeneity observed in this meta-analysis. Unfortunately, this issue was not tackled in many studies, whereas in others, mood was measured by means of different instruments, which prevented us from exploring the influence of between-group differences in depression/mania symptoms on the effect sizes observed for social cognition. Furthermore, it was proposed that ideally, measurements of euthymia should involve some period of prospective verification, and residual mood symptoms should be measured and controlled for statistically in data analysis (3). It is therefore worthy of note that bipolar patients scored significantly higher than controls on mood rating scales in most of the studies reviewed, and very few endeavors have been undertaken to covary out the influence of mood symptoms on social-cognitive performance. Another possible shortcoming concerns the small number of studies including self-report measures of depressive symptomatology. Indeed, one of the studies documenting large effect sizes for ToM impairments (73) reported that patients with BD, although fulfilling stringent criteria of euthymia, had some modest self-rated symptoms of mood that separated them significantly from healthy controls.

On the other hand, the association between traditional neurocognitive impairments and social cognition was reported in different studies. In fact, in the three largest studies exploring ToM in patients with euthymic BD, impairments in attention and executive functions were a confounding factor in patient–control differences for mindreading performance (34, 35, 37). We were not able to assess the possible effect of cognitive domains that have been shown to be impaired in patients with BD, such as attention and executive functioning (3–6), on the observed effect sizes because neurocognitive measures were not available together with social cognition tasks in sufficient studies. Finally, the role of medication became evident in a previous study that found that the exposure to antipsychotics and benzodiazepines was associated with ToM and emotion processing impairments (34). Similarly, previous studies focusing on healthy volunteers have reported the negative influence of benzodiazepines on the recognition of human facial expressions (64, 65, 96). In the current meta-analysis, studies with higher percentages of patients taking antipsychotics tended to report higher effect sizes for emotion processing, but this association failed to reach statistical significance. However, these results are limited by the small number of studies included in the meta-regression. In addition to the effect of these moderators, another major concern relies on the fact that some studies reported that the extension and severity of cognitive impairments may be heterogeneous among euthymic bipolar patients (8, 97, 98). These findings suggest that studies reporting mean values of cognitive functioning in BD might be failing to recognize that a subgroup of bipolar patients is demonstrating most of the impairment. Therefore, further studies are needed to explore extension of social-cognitive impairments among patients with euthymic BD.

In contrast, there is some preliminary evidence for emotion processing dysfunction being a trait marker and a candidate endophenotype for BD. Brotman et al. (99) have yielded evidence for emotion processing impairments in subjects at risk of the illness by virtue of having a parent and/or sibling with the diagnosis. Furthermore, Surguladze et al. (84) explored the neural correlates of emotion processing in patients with BD and their unaffected first-degree relatives, finding a discrete pattern of exaggerated brain activity in response to either happy or fearful faces in both patients and their relatives. The results of this study indicated that the overactivation of medial prefrontal cortex and subcortical structures (putamen and amygdala) in response to a facial emotion processing task may represent a neurobiological abnormality associated with genotypic variation conferring liability for BD. A critical approach to disentangling the neuropsychological impairments related to the pathophysiology of BD from those that may be secondary to affective symptoms and treatment iatrogenic effects consists in exploring whether these deficits are found among individuals at high risk of BD but not yet affected. Additionally, this approach could contribute to the identification of neurocognitive endophenotypes for BD, traits that are more proximal to the genetic substrate than are diagnostic categories (100).

The first limitation of the current study is the heterogeneous nature of social cognition tasks and the lack of information about the psychometric properties of the different neuropsychological tests employed. Thus, although we believe this is an important contribution to the knowledge on social-cognitive functioning in BD, further investigation is needed to determine which aspects of ToM are impaired as well as the effect sizes of the differences between patients and healthy controls. Second, the paucity of studies on social cognition and the scant available data regarding confounding variables prevented us from conducting individual task analyses as well as more detailed meta-regression analyses. The complete profile of social-cognitive impairments, as well as the influence of neurocognitive deficits, therefore remains to be determined until sufficient data become available. Besides, the assessment of decision-making abilities was performed using the Iowa gambling task in most studies. It has been suggested that this task may not be sensitive enough to detect defective decision-making in BD, and the development of new paradigms is therefore needed (101). Furthermore, although evidence supports that choices of patients with euthymic BD under conditions of uncertainty are not characterized by a generalized tendency to risk taking, some differences in reaction time, total money earned and cognitive style have been documented (41, 76, 77).

The identification of social-cognitive deficits in patients with euthymic BD provides a number of targets for future investigation. First, research regarding the different components of social cognition and their operationalization is necessary, as well as further investigation on the psychometric properties of the instruments for the assessment of this domain. Second, different aspects of social cognition should be explored in larger samples of euthymic patients to determine the specificity and extent of social-cognitive deficits. Third, a consensus battery assessing more thoroughly the wide range of social-cognitive components should be agreed and included in research studies. Fourth, the knowledge on the relative impact of medication and neurocognitive deficits on social-cognitive functioning must be broadened. Fifth, familiar studies exploring ToM and emotion processing are necessary to determine whether deficits in these domains might be considered as trait markers of the illness and candidate endophenotypes to BD. If ToM deficits prove to be an endophenotype for BD, this knowledge could ultimately aid in efforts aimed at identifying risk-related genes for the illness, as well as in prevention and early intervention. Sixth, the clinical relevance of social-cognitive impairments in terms of their influence in functional outcome must be assessed. To the best of our knowledge, only three studies have explored this relationship, providing mixed results (34, 36, 102). Finally, a better understanding of the extent of ToM and emotion processing dysfunction and the role of moderators on such domain would help to develop preventative and therapeutic strategies – such as the evaluation of a trade-off between clinical benefits and costs related to medication options- to arrest social-cognitive dysfunction.

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