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SYSTEMATIC REVIEW

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Correlation between emotion dysregulation and mood symptoms of bipolar disorder: A systematic review and meta-analysis

Vincenzo Oliva[1,2,3,4] | **Michele De Prisco**[1,2,5] | **Giovanna Fico**[1,2,3] | **Chiara Possidente**[1,2,3,4] | **Lydia Fortea**[1,2,3] | **Laura Montejo**[1,2,3,5] | **Gerard Anmella**[1,2,3,5] | **Diego Hidalgo-Mazzei**[1,2,3] | **Iria Grande**[1,2,3,5] | **Andrea Murru**[1,2,3] | **Michele Fornaro**[6] | **Andrea de Bartolomeis**[6] | **Alyson Dodd**[7] | **Giuseppe Fanelli**[4,8] | **Chiara Fabbri**[4,9] | **Alessandro Serretti**[4] | **Eduard Vieta**[1,2,3,5] | **Joaquim Radua**[1,2,3,5,10,11]

[1]Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), Barcelona, Spain

[2]Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain

[3]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[4]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

[5]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

[6]Section of Psychiatry, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy

[7]Department of Psychology, Faculty of Health & Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK

[8]Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

[9]Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[10]Department of Clinical Neuroscience, Centre for Psychiatric Research and Education, Karolinska Institutet, Stockholm, Sweden

[11]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Correspondence
Vincenzo Oliva and Eduard Vieta, Bipolar and Depressive Disorders Unit, Department of Psychiatry and Psychology, Institute of Neurosciences, Hospital Clínic Barcelona, C. de Villarroel, 170, 08036 Barcelona, Catalonia, Spain.
Email: violiva@recerca.clinic.cat and evieta@clinic.cat

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Abstract

Background: Emotion dysregulation (ED) is a transdiagnostic construct characterized by difficulties regulating intense emotions. People with bipolar disorder (BD) are more likely to show ED and use maladaptive emotion regulation strategies than adaptive ones. However, little is known about whether ED in BD is a trait or it is rather an epiphenomenon of mood symptoms.

Methods: We conducted a systematic review and meta-analysis of the evidence across major literature databases reporting correlations between measures of emotion regulation (overall ED and different emotion regulation strategies) and measures of depressive and (hypo)manic symptoms in BD from inception until April 12th, 2022.

Results: Fourteen studies involving 1371 individuals with BD were included in the qualitative synthesis, of which 11 reported quantitative information and

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were included in the meta-analysis. ED and maladaptive strategies were significantly higher during periods with more severe mood symptoms, especially depressive ones, while adaptive strategies were lower.

Conclusion: ED significantly correlates with BD symptomatology, and it mainly occurs during mood alterations. ED may be a target for specific psychotherapeutic and pharmacological treatments, according to precision psychiatry. However, further studies are needed, including patients with mood episodes and longitudinal design, to provide more robust evidence and explore the causal direction of the associations.

KEYWORDS

bipolar disorder, depressive symptoms, emotion dysregulation, emotion regulation, manic symptoms

1 | INTRODUCTION

Emotion regulation (ER) is the process by which individuals influence their emotional experiences, including the generation, intensification, or reduction of emotions, as well as the duration and expression of those emotions.[1] ER involves a set of strategies that individuals employ to manage and modulate their emotions in order to adapt to various situations and meet goals.[2] These strategies are commonly classified into two categories: adaptive strategies (i.e., acceptance, active coping, and cognitive reframing) and maladaptive strategies (i.e., negative focus, negative or positive rumination, risk-taking behaviors, suppression, and dampening).[3] The rigid application of certain ER strategies, or the use of only maladaptive ones, leads to emotion dysregulation (ED).[4] In a large conceptual framework,[5] ED is a multidimensional construct involving a lack of awareness, understanding and acceptance of emotions, the capacity to embrace or accept negative emotions as an integral part of engaging in meaningful pursuits in life, reduced access to adaptive and situationally appropriate strategies to modulate emotional responses, and an inability to behave in accordance with desired goals and control impulsive behaviors when experiencing intense emotions.[6] ED is considered as trans-diagnostic, occurring across different mental disorders with varying degrees of pervasiveness.[7] Neuroimaging studies have implicated several brain regions in the genesis of emotions and in ER, with a particular emphasis on the prefrontal cortex and amygdala.[8] Although ED is generally regarded as a dispositional tendency (i.e., trait-ED),[9] it has been proposed that ED may undergo changes based on psychopathological states (i.e., state-ED).[10] Indeed, patients with major depressive disorder (MDD) or eating disorders in a remission phase adopt better ER strategies or manifest lower levels of ED compared to people with current clinically significant symptoms.[11,12]

Summations

- Emotion dysregulation, a transdiagnostic construct, is present in bipolar disorder and is directly correlated to its psychopathology.
- Depressive symptoms are moderately correlated to emotion dysregulation, and are related to all type of emotion regulation strategies considered.
- Manic symptoms appeared less strongly correlated to emotion dysregulation and emotion regulation strategies, however, this result could be due to characteristics of the included studies.

Limitations

- Additional primary studies are warranted to allow extensive sub-groups and meta-regressions, especially in case of high heterogeneity.
- Correlation with mixed characteristics could not be addressed due to the lack of data from the primary studies to date.
- Correlations cannot confirm causation.

Existing systematic reviews (SR) and meta-analyses (MA) showed that patients diagnosed bipolar disorder (BD) are particularly prone to higher ED levels.[13,14] BD is a severe chronic mental illness characterized by changes in synaptic plasticity and neuronal connectivity resulting from several genetic, epigenetic, and environmental factors.[15–17] The brain regions with key roles in ER, present an altered activation in BD.[18] Both a reduced activation of the prefrontal circuits and hyperactivation of the limbic structures, including the amigdala, during emotional tasks were found in patients with BD.[19–21] As BD is characterized by acute mood episodes (i.e., (hypo)manic and depressive), with intercritical periods of sub-syndromic symptomatology,[22] this raises the question of how much ED in BD is related to current mood polarity (state) or to the diagnosis itself instead (trait). It is noteworthy that hypoactivation of prefrontal circuits remained stable over time in patients with BD in remission, representing a trait-marker of persistent difficulties in ER,[23] whereas state-specific alterations in activation of the amygdala were observed in longitudinal neuroimaging studies in patients with BD during acute phases.[24,25] In addition, trait and state differences have been described in patients with BD regarding dimensions of cognitive function,[26–29] while other features such as impulsivity have been suggested as trait characteristics.[30] Thus, it may be reasonable to hypothesize that ED and the use of ER strategies may change according to mood states in BD. Previous SR and MA on the topic have encountered limitations in investigating this phenomenon by categorizing patients based on their actual mood episode.[13] An alternative approach is to quantify correlations between ED and psychopathological measures.[31–34] Considering the differences in the phenomenology and clinical outcomes of the (hypo)manic and depressive dimensions,[35] this approach can help to delineate which ED features that are particularly relevant and useful for the development of new transdiagnostic treatments according to precision psychiatry, both psychotherapeutic and pharmacological.[36]

The present SR and MA aims to fill the knowledge gap on the relationship between ED and BD psychopathology. We assessed and quantified the correlations between validated measures of overall ED, maladaptive ER strategies, adaptive ER strategies[3] and validated measures of both depressive and (hypo)manic symptomatology in patients with BD. The considered maladaptive ER strategies were negative focus, negative and positive rumination, risk-taking behaviors, suppression, and dampening, while adaptive strategies were acceptance, adaptive coping, and cognitive reframing.[3]

2 | MATERIALS AND METHODS

The present SR and MA followed the "*Meta-analysis of Observational Studies in Epidemiology*" (MOOSE) reporting guideline[37] and the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA) 2020 guideline.[38] The checklists of both guidelines are reported in Supplementary materials—Appendix 1 and 2. In addition, the study protocol was registered in the "*International Prospective Register of Systematic Reviews*" (PROSPERO) (https://www.crd.york.ack/PROSPERO/), with protocol number CRD42022325738. Protocol amendments are reported in the Supplementary materials—Appendix 3.

2.1 | Search strategy

A systematic literature search (search terms appended in Supplementary materials—Appendix 4) was implemented on PubMed/MEDLINE, EMBASE, Scopus, and PsycINFO from inception until April 12th, 2022. In addition, the references of the included articles, books, and other relevant materials were also manually searched and inspected to include additional original studies not captured by the search strings.

2.2 | Eligibility criteria

We considered for inclusion original articles: (a) published in a peer-reviewed journal; (b) including people with BD, according to validated diagnosis criteria, that is, *Diagnostic and Statistical Manual of mental disorders* (DSM) criteria,[39–41] or *International Statistical Classification of Diseases and Related Health Problems* (ICD) criteria[42]; (c) assessing the severity of depressive or (hypo)manic symptoms of BD with objective and validated instruments adopting a metric scale; (d) providing continuous measures of ED according to an objective validated instrument; (e) reporting the correlation coefficients between measures of depressive or (hypo)manic symptoms of BD and measures of ED or measures of each ER strategy. Contact with the authors was attempted if this information was unavailable in the original article. No language and age restrictions were applied.

Studies were excluded if they: (a) were reviews, clinical cases, abstracts, letters to the editor failing to report original data, conference proceedings, or study protocols; (b) only included non-human samples; (c) were interventional studies not providing baseline data.

2.3 | Study selection and data extraction

The titles and abstracts of the articles obtained from the search strings in the respective databases were appraised based on the previously defined inclusion and exclusion criteria. After excluding those irrelevant, the potentially eligible articles were examined by reading their full texts. When available, the following data were obtained from included studies: first author, publication year, study design, study setting, country, and geographical region in which the study was conducted, sample size, mean sample age with its standard deviation (SD), % of females, information regarding the diagnostic criteria and tool used, duration of illness, age at onset of BD, % of BD type (BD-I or BD-II), mood state (% of patients in the euthymic state, (hypo)manic or depressive episodes), % of patients in psychopharmacological therapy, psychiatric and medical comorbidities, the instrument used to measure depressive and (hypo)manic symptoms, mean scores with their SD obtained on symptoms severity scales, the tool used to measure ED, mean scores with their SD obtained on ED severity scales, the correlation coefficient between ED measures and depressive symptoms of BD, the correlation coefficient between ED measures and (hypo)manic symptoms of BD. If the studies reported data only as part of figures, the WebPlotDigitizer program (https://automeris.io/WebPlotDigitizer/) was used to extract this information manually. If the data were not fully available in the published article, their authors were contacted up to two times to ask for the necessary data.

Two investigators (VO and MDP) conducted all the steps described independently. Discrepancies were resolved through consensus with a third senior author (GF).

2.4 | Quality control

The *Risk of Bias* was independently assessed by two investigators (VO and MDP) by adopting the "*Newcastle-Ottawa Scale*" (NOS),[43] which was used to evaluate the quality of the included observational studies. Discrepancies were resolved through consensus with a third senior author (GF). The scores obtained were then converted according to the standards "*Agency for Healthcare Research and Quality*" (AHRQ) as described in previous studies.[44]

2.5 | Statistical analysis

All statistical analyses were conducted using R version 4.1.2.[45] We conducted separate MAs for correlations between measures of ED and measures of depressive and (hypo)manic symptoms, as well as the correlations between measures of each ER strategy and measures of depressive and (hypo)manic symptoms. The Pearson's r coefficients were meta-analyzed using the "*metafor*"[46] R-package, within a random-effect model, with a *restricted maximum-likelihood estimator* of the heterogeneity.[47] Finally, the interpretation was based on predefined conventional cutoffs as follows: values between 0 and 0.3 indicate a weak positive effect, values between 0.3 and 0.7 show a moderate positive effect, and values above 0.7 indicate a strong positive effect.[48]

Heterogeneity analyses were assessed using Cochran's Q test,[49] and I^2 statistic (with 0% indicating no observed heterogeneity, while 25%, 50%, and 75% defining the thresholds for low, moderate, and high I^2, respectively).[50] Additionally, prediction intervals were estimated.[51] Further analyses were conducted to investigate: (a) each study's influence on the overall effect size estimation; (b) the potential role of specific factors on ED; and (c) the source(s) of heterogeneity in case of Cochran's Q test p-value $< .10$[49] or $I^2 > 50\%$.[50] In detail, leave-one-out sensitivity analyses were performed by omitting one study at a time. Sensitivity analyses were also conducted considering the geographical region where the studies were conducted. Meta-regression analyses were conducted considering as potential modulators mean sample age, % of females, % of patients diagnosed with BD-I, % of euthymic patients, % of patients with a depressive episode, % of patients with a (hypo)manic episode, the mean scores of the ED rating scales, the mean scores of the depressive symptoms' rankings, and the mean scores of the (hypo)manic symptoms' scales. If studies provided data using different rating scales, the values were scaled before the related meta-regression. The presence of publication bias was visually assessed by drawing funnel plots; the Egger regression asymmetry test was performed to test numerically for potential publication bias.[52,53] Statistical significance was evaluated two-sided at the 5% threshold.

3 | RESULTS

3.1 | Study characteristics

Overall, 13,826 records were identified through our search strategy, returning 6799 hits after a supervised duplicate removal. Of these, 6335 were excluded after title and abstract screening, 446 after reading the full texts, and five because they were not retrieved even after contacting the authors, resulting in 13 studies[54–66] that fulfilled our inclusion criteria. Finally, one additional

study[67] was identified by reviewing the references of included papers, resulting in 14 studies included in the qualitative synthesis, 10 of which[54–57,59,60,62–65,67] were included in the quantitative synthesis. Four studies[56,57,62,68] did not provide data for the quantitative synthesis in the main text, but the correlations were provided after contacting the corresponding authors. Overall, the studies included in the MA provided 84 unique correlations between measures of ED and depressive symptoms and 82 univocal correlations between measures of ED and (hypo)manic symptoms. The PRISMA flowchart is shown in Figure 1. The characteristics of included studies are provided in Table 1.

A comprehensive list of excluded studies, accompanied by the respective reasons for their exclusion, is also provided in the Supplementary materials—Appendix 5. Additional information regarding the included studies, including details on the scales and tasks used to assess ED and depressive and (hypo)manic symptoms, along with mean scores, measures of variance, and correlations, as well as information on psychiatric comorbidities and psychiatric pharmacotherapy, can be found in the Supplementary materials—Appendix 6–12.

3.2 | Meta-analyses results

3.3 | Main analyses

Separate MA were conducted to quantify correlations between depressive symptoms of BD and measures of ED and specific ER strategies, and correlations between (hypo)manic symptoms of BD and measures of ED and specific ER strategies. MA were possible for all adaptive

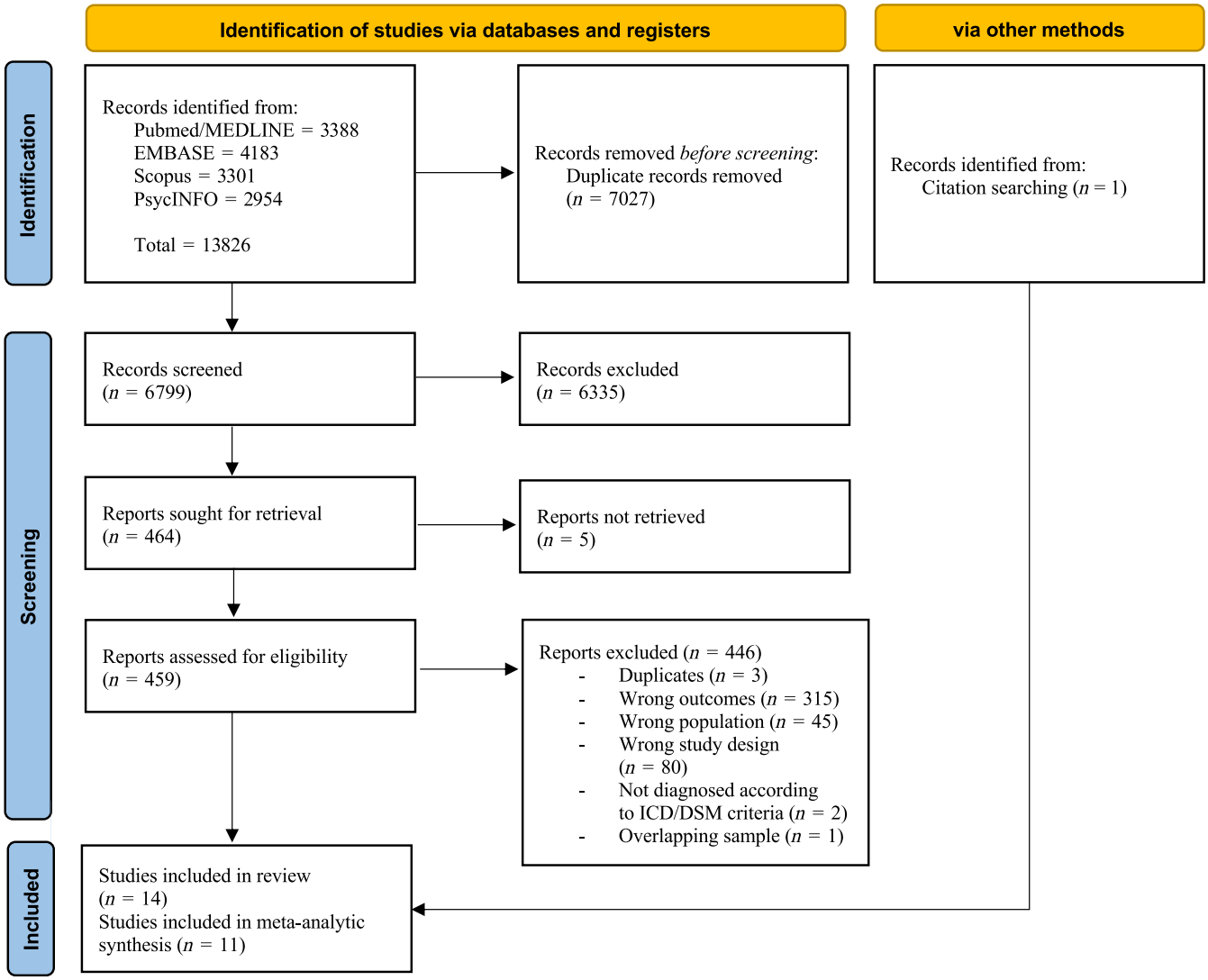

FIGURE 1 PRISMA flowchart, 2020 edition, adapted.

TABLE 1 Characteristics of included studies.

Country/ Region	Study/design	*n.*	Mean Age (SD)	% Female	BD-I, n. (%)	Mood state (%)	Criteria used for BD diagnosis (instrument)	Instrument to assess affective symptoms	ER strategies explored	Instrument to assess ED	Quality of the study (NOS)
Australia/ Oceania	Fletcher et al.[67]/ longitudinal	151	42.5 (10)	62.9	67 (45.7)	Euthymic: 53.5 Manic: 16.5 Depressive: 30.7	DSM-IV (MINI)	ISS	Negative Focus, Cognitive Reframing, Dampening, Positive Rumination, Negative Rumination, Adaptive coping, Risk-taking	CERQ, RPA, RSQ	6/FAIR
Australia/ Oceania	Fletcher et al.[54]/ cross-sectional	302	44 (11.8)	70.5	242 (80.1)	Euthymic: 100%	DSM-IV (MINI)	QIDS-SR, YMRS	Overall emotion dysregulation	DERS-16	7/FAIR
Australia/ Oceania	Green et al.[55]/ cross-sectional	105	52.39 (14.1)	68.6	105 (100)	Euthymic: NA Manic: NA Depressive: NA	DSM-IV (DIGS)	DASS, HPS	Acceptance, Cognitive reframing, Negative focus, Negative rumination,	CERQ	6/FAIR
Iran/Asia	Khosravani et al.[56]/cross-sectional	300	33.08 (10.29)	100	NA	Manic: 35.7 Depressive: 64.3	DSM-V (SCID-5)	BDRS, YMRS	Acceptance, Adaptive coping, Risk-taking, Overall emotion dysregulation	DERS	6/FAIR
USA/North America	Linke et al.[57]/ cross-sectional	36	16.8 (3.27)	47.2	15 (41.7)	Euthymic: 86.1 Manic: 13.9	DSM-V (K-SADS)	CDRS, YMRS	Acceptance, Adaptive coping, Risk-taking, Overall emotion dysregulation	DERS	4/FAIR
USA/North America	Peckham et al.[58]/ cross-sectional	59	35.24 (11.56)	59.6	59 (100)	Euthymic: NA Manic: NA Depressive: NA	DSM-IV (MINI)	HAM-D, YMRS	Cognitive reframing, Negative rumination, Suppression	ERQ, RRS	5/FAIR
Australia/ Oceania	Rowland et al.[59]/ cross-sectional	97	51.26 (12.1)	62.9	97 (100)	Euthymic: NA Manic: NA Depressive: NA	DSM-IV (SCID-I)	DASS, HPS	Acceptance, Cognitive reframing, Negative focus, Negative rumination	CERQ	6/FAIR
Turkey/ Asia	Saglam et al.[60]/ cross-sectional	64	NA	NA	NA	Euthymic: 48.4 Manic: 18.8 Depressive: 32.8	DSM-V (SCID-I)	HAM-D, YMRS	Acceptance, Adaptive coping, Risk-taking, Overall emotion dysregulation	DERS	5/FAIR
USA/North America	Tabak et al.[61]/ cross-sectional	38	43.47 (11.38)	42.1	NA	Euthymic: 76.3	DSM-IV (SCID-I)	HAM-D, YMRS	Acceptance, Adaptive coping, Negative rumination, Overall emotion dysregulation	TMMS	4/FAIR

(Continues)

TABLE 1 (Continued)

Country/ Region	Study/design	*n.*	Mean Age (SD)	% Female	BD-I, n. (%)	Mood state (%)	Criteria used for BD diagnosis (instrument)	Instrument to assess affective symptoms	ER strategies explored	Instrument to assess ED	Quality of the study (NOS)
USA/North America	Van Meter and Youngstrom[62]/ cross-sectional	23	NA	NA	11 (47.8)	Euthymic: 86.9 Depressive: 13.1	DSM-V (MINI)	BD-I HCL	Acceptance, Cognitive reframing, Negative focus, Negative rumination, Overall emotion dysregulation	CERQ	6/FAIR
Australia/ Oceania	Van Rheenen et al.[63]/cross-sectional	50	38.44 (13.02)	66	38 (76)	Euthymic: 34 Manic: 16 Depressive: 17	DSM-IV (MINI)	MADRS, YMRS	Acceptance, Adaptive coping, Risk-taking, Overall emotion dysregulation	DERS	6/FAIR
Australia/ Oceania	Van Rheenen et al.[64]/cross-sectional	65	37.68 (11.46)	48.5	NA	Euthymic: 68.2	DSM-IV-TR (MINI)	MADRS, YMRS	Acceptance, Adaptive coping, Risk-taking, Overall emotion dysregulation	DERS	5/FAIR
Germany/ Europe	Wolkenstein et al.[65]/cross-sectional	42	40.86 (12.79)	61.9	26 (62)	Euthymic: 100	DSM-IV (SCID-I)	QIDS, SRMI	Acceptance, Negative focus	CERQ	4/FAIR
China/Asia	Wong et al.[66]/ cross-sectional	39	24.4 (6.2)	59	39 (100)	Euthymic: 100	DSM-IV (SCID-I)	HAM-D, YMRS	Risk-taking	BART	5/FAIR

Abbreviations: BART, Balloon Analog Risk Task; BD, Bipolar Disorder; BD-I, Beck Depression Inventory; BDRS, Bipolar Depression Rating Scale; CDRS, Children's Depression Rating Scale; CERQ, Cognitive Emotion Regulation Questionnaire; DASS, Depression Anxiety Stress Scale; DERS, Difficulties in Emotion Regulation Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ED, Emotion Dysregulation; ER, Emotion Regulation; ERQ, Emotion Regulation Questionnaire; HAM-D, Hamilton Depression Rating Scale; HCL, Hypomanic Checklist; MADRS, Montgomery-Asberg Depression Rating Scale; HPS, Hypomanic Personality Scale; ISS, Internal State Scale; K-SADS, Schedule for Affective Disorders and Schizophrenia MINI, The Mini-International Neuropsychiatric Interview; n., number of the total sample: NA, not applicable; QIDS-SR, Quick Inventory of Depressive Symptomatology Self Report; RPA, Responses to Positive Affect Questionnaire; RRS, Ruminative Response Scale; RSQ, Response Styles Questionnaire; SCID, Structured Clinical Interview for DSM Disorders; SD, standard deviation; SRMI, Self-reported severity of manic symptoms; TMMS, Trait Meta-Mood Scale; YMRS, Young Mania Rating Scale.

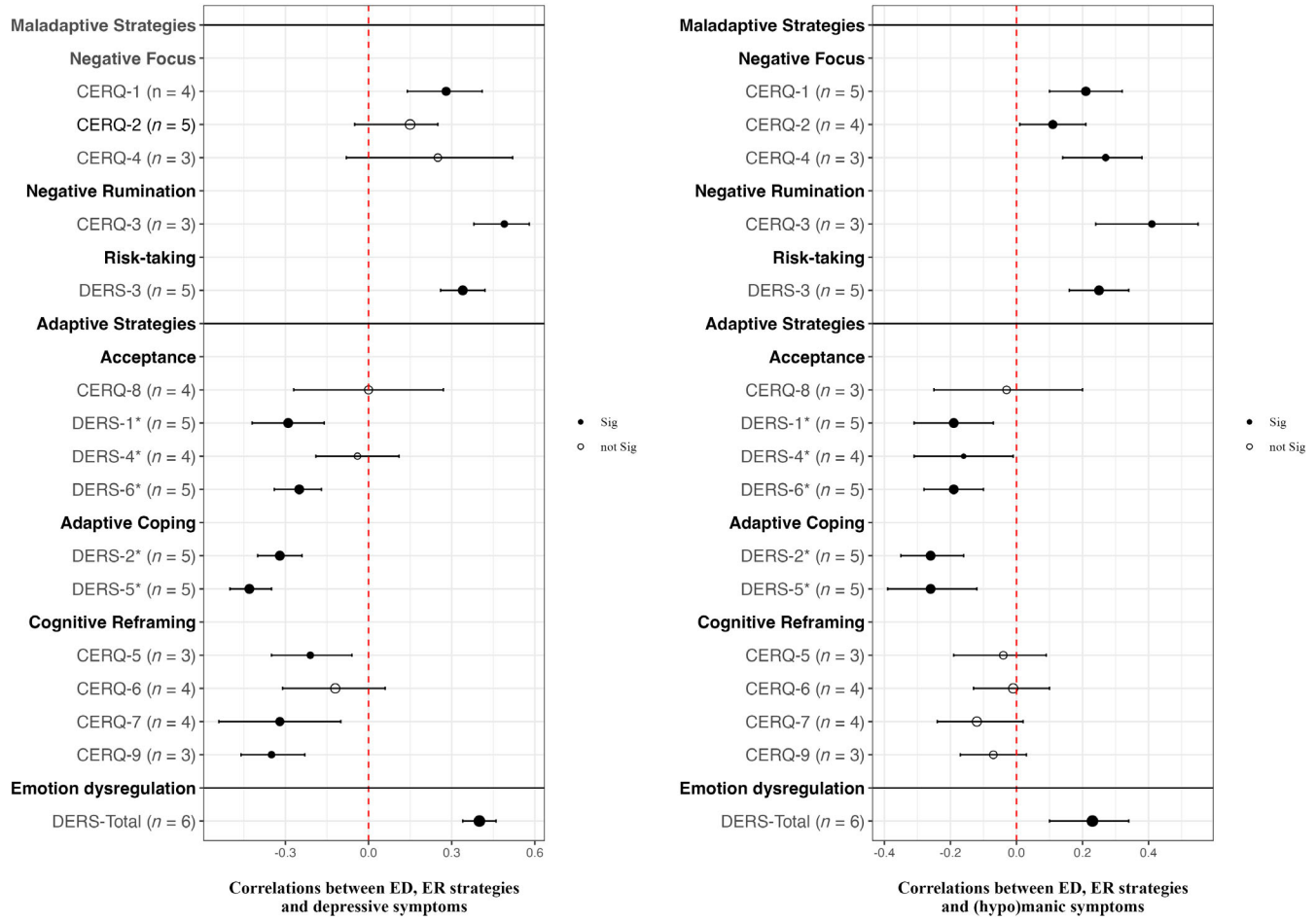

FIGURE 2 Overall results of the meta-analysis. CERQ, Cognitive Emotion Regulation Scale; CERQ-1, self-blame; CERQ-2, blaming others; CERQ-3, rumination; CERQ-4, catastrophizing; CERQ-5, putting into perspective; CERQ-6, positive refocus; CERQ-7, positive reappraisal; CERQ-8, acceptance; CERQ-9, focus on replanning; DERS, Difficulties in Emotion Regulation Scale; DERS-1, non-acceptance; DERS-2, goals; DERS-3, impulse; DERS-4, awareness; DERS-5, strategies; DERS-6, clarity; DERS-Total, total score; n, total number of studies included in the meta-analysis; Sig, significant; not Sig, not significant. The size of the dots is proportional to the sample size of BD patients included in the meta-analysis. *The ES score of these items has been inverted to present graphically coherent results since the scale initially measures the individual's difficulties in adopting that emotion regulation strategy.

ER strategies and three of the six maladaptive ER strategies considered (i.e., negative focus, negative rumination, and risk-taking behaviors).

Results on the direction and magnitude of the meta-analytic evidence of associations are illustrated in Figures 2 and 3 and reported in Table 2. Forest plots are reported in the Supplementary materials—Appendix 13 and 14.

Overall, both depressive and (hypo)manic symptoms were significantly associated with increased ED, the former with moderate effect size ($r = .40$) and the latter with a weak effect size ($r = .23$). When examining specific ER strategies, no strong correlations were observed. There were moderate correlations between depressive symptoms and certain maladaptive strategies, namely "negative rumination" ($r = .49$) and "risk-taking" ($r = .34$). Depressive symptoms were also moderately correlated with a decrease in the scores of the subscales "goals" and "strategies" of the adaptive strategy "adaptive coping" ($r = -.32$ and $-.43$, respectively), as well as the subscales "positive reappraisal" and " focus on replanning" of the adaptive strategy "cognitive reframing" ($r = -.32$ and $-.35$, respectively). On the other hand, (hypo)manic symptoms were only moderately associated with an increase in "negative rumination" ($r = .41$). The other correlations were weak or not significant.

3.4 | Sensitivity analyses

Leave-one-out sensitivity analyses and sensitivity analyses by geographical region did not change the patterns

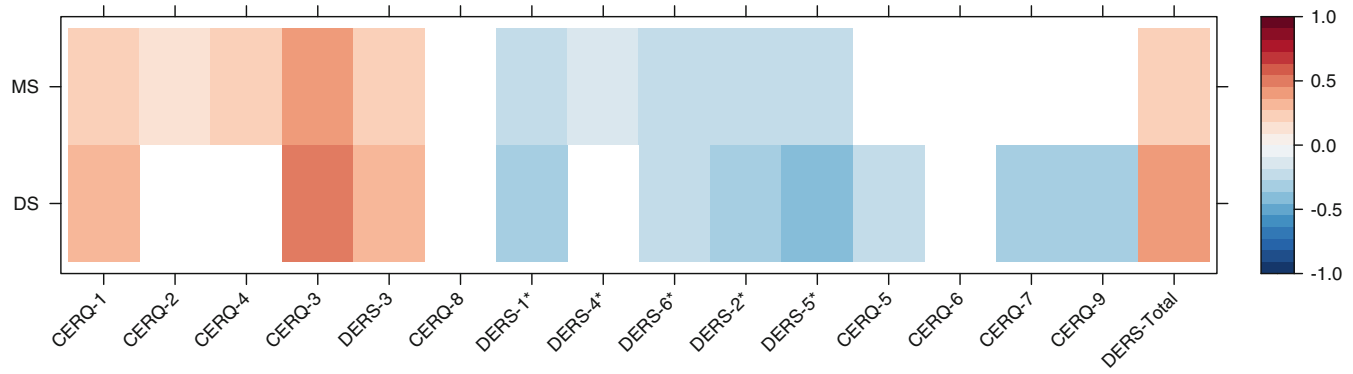

FIGURE 3 , Heatmap of significant effect sizes included in the meta-analysis. CERQ, Cognitive Emotion Regulation Scale; CERQ-1, self-blame; CERQ-2, blaming others; CERQ-3, rumination; CERQ-4, catastrophizing; CERQ-5, putting into perspective; CERQ-6, positive refocus; CERQ-7, positive reappraisal; CERQ-8, acceptance; CERQ-9, focus on replanning; DERS, Difficulties in Emotion Regulation Scale; DERS-1, non-acceptance; DERS-2, goals; DERS-3, impulse; DERS-4, awareness; DERS-5, strategies; DERS-6, Clarity; DERS-Total, total score; DS, depressive symptoms; MS, manic symptoms. *The ES score of these items has been inverted to present graphically coherent results since the scale initially measures the individual's difficulties in adopting that emotion regulation strategy.

of the correlations between ED and depressive and (hypo)manic symptoms. When utilized to examine heterogeneity across ER strategies, the analysis detected a substantial impact of the studies by Green et al., Wolkenstein et al, and Rowland et al. and of the studies conducted in Oceania on the associations between depressive symptoms and specific ER strategies (for further details see results of sensitivity analysis in the Supplementary materials—Appendix 13 and 14).

3.5 | Meta-regression analyses

Results of meta-regressions with related bubble plots are presented in the Supplementary materials—Appendix 13 and 14.

Overall, none of the considered modulators influenced the correlations between depressive symptoms and ED. On the other hand, a higher percentage of euthymic patients ($\beta = -.231$) significantly decreased the correlation between (hypo)manic symptoms and ED. Conversely, a higher percentage of patients experiencing a depressive episode ($\beta = .378$), as well as higher mean scores on the ED and (hypo)manic symptoms scales ($\beta = .004$ and $\beta = .031$, respectively) significantly increased the correlation between (hypo)manic symptoms and ED.

When meta-regressions were used to examine heterogeneity across specific ER strategies, the following findings were observed: (i) older age ($\beta = .05$), a higher percentage of patients diagnosed with BD-I ($\beta = 1.034$), and higher mean scores of depressive and (hypo)manic symptoms ($\beta = .328$ and $\beta = .048$) significantly increased the correlation between depressive symptoms and the "acceptance" subscale; (ii) the increase in the percentage of female individuals ($\beta = 5.258$) significantly weakened the negative correlation between depressive symptoms and the "positive refocus" subscale; (iii) the decrease in mean scores of the ED rating scales ($\beta = -.072$) significantly increased the correlation between (hypo)manic symptoms and "acceptance" subscale.

3.6 | Risk of bias

The overall quality of included studies was fair. The average quality rating (theoretical range between 0 and 8) of the included studies was 5.36 (SD = 0.93; range = 4–7) (see the agreed quality grades of each study in Table 1 and a report of each general score in the Supplementary materials—Appendix 15).

3.7 | Publication bias

The visual inspection of the funnel plots and the Egger tests (see in the Supplementary materials—Appendix 16) did not suggest publication bias for most of the associations considered. Publication bias was detected for the associations between depressive symptoms and the subscales "non-acceptance" (Egger test: $z = -2.3680$, $p = .0179$) and "positive reappraisal" (Egger Test: $z = -2.8415$, $p = .0045$).

4 | DISCUSSION

The present SR and MA aimed to describe the relationship between ED, specific maladaptive and adaptive ER

TABLE 2 Results of meta-analyses in detail.

ED scale adopted	ED subscale	Studies, *n*	BD patients, *n* (E/D/M/NA, %)	Pearson's r	95% CI	*p*-Value	95% PI	I^2 (%)	Q-test *p*-value
Depressive symptoms									
Overall measures of emotion dysregulation									
DERS	Total score	6	771 (51/30/16/3)	**0.40**	**0.34, 0.46**	**7.14e-32**	**0.34, 0.46**	0	0.87
Maladaptive emotion regulation strategies									
Negative focus									
CERQ	1-Self blame	4	376 (25/15/10/50)	**0.28**	**0.14, 0.41**	**7.38e-05**	**0.06, 0.46**	37.5	0.19
CERQ	2-Blaming others	5	428 (34/12/6/48)	0.15	−0.05, 0.35	0.15	−0.27, 0.52	72.8	0.02
CERQ	4-Catastrophizing	3	225 (9/1/0/90)	0.25	−0.08, 0.52	0.14	−0.34, 0.69	80.5	0.01
Negative rumination									
CERQ	3-Rumination	3	225 (9/1/0/90)	**0.49**	**0.38, 0.58**	**6.08e-15**	**0.38, 0.58**	0	0.51
Risk taking									
DERS	3-Impulse	5	472 (20/49/27/4)	**0.34**	**0.26, 0.42**	**2.24e-14**	**0.26, 0.42**	0	0.51
Adaptive emotion regulation strategies									
Acceptance									
CERQ	8-Acceptance	4	267 (23/1/0/76)	0	−0.27, 0.27	0.98	−0.50, 0.50	76.9	0.01
DERS	1-Acceptance (reverse)	5	472 (20/49/27/4)	**−0.29**	**−0.42, −0.16**	**1.96e-05**	**−0.49, −0.07**	34.8	0.23
DERS	4-Awareness (reverse)	4	172 (54/22/12/12)	−0.04	−0.19, 0.11	0.61	−0.19, 0.11	0	0.95
DERS	6-Clarity (reverse)	5	472 (20/49/27/4)	**−0.25**	**−0.34, −0.17**	**3.31e-08**	**−0.34, −0.16**	0	0.32
Adaptive coping									
DERS	2-Goals (reverse)	5	472 (20/49/27/4)	**−0.32**	**−0.40, −0.24**	**1.01e-12**	**−0.40, −0.24**	0	0.98
DERS	5-Strategies (reverse)	5	472 (20/49/27/4)	**−0.43**	**−0.50, −0.35**	**1.09e-22**	**−0.50, −0.35**	0	0.92
Cognitive reframing									
CERQ	5-Putting into perspective	3	225 (9/1/0/90)	**−0.21**	**−0.35, −0.06**	**5.29e-03**	**−0.38, −0.03**	16.7	0.35
CERQ	6-Positive refocus	4	376 (25/15/10/50)	−0.12	−0.31, 0.06	0.19	−0.44, 0.22	65.2	0.04
CERQ	7-Positive reappraisal	4	376 (25/15/10/50)	**−0.32**	**−0.54, −0.10**	**4-06e-03**	−0.63, 0.10	74.6	0.04
CERQ	9-Focus on replanning	3	225 (9/1/0/90)	**−0.35**	**−0.46, −0.23**	**6.86e-08**	**−0.46, −0.23**	0	0.35
Manic symptoms									
Overall measures of emotion dysregulation									
DERS	Total score	6	762 (52/27/18/3)	**0.23**	**0.10, 0.34**	**4.76e-04**	**0.10, 0.34**	53.4	0.03

(Continues)

TABLE 2 (Continued)

ED scale adopted	ED subscale	Studies, *n*	BD patients, *n* (E/D/M/NA, %)	Pearson's r	95% CI	*p*-Value	95% PI	I^2 (%)	Q-test *p*-value
Maladaptive emotion regulation strategies									
Negative focus									
CERQ	1-Self blame	5	428 (34/12/6/48)	**0.21**	**0.10, 0.32**	**2.38e-04**	**0.05, 0.35**	18.3	0.16
CERQ	2-Blaming others	4	376 (27/13/7/53)	**0.11**	**0.01, 0.21**	**0.04**	**0.01, 0.21**	0	0.99
CERQ	4-Catastrophizing	3	225 (9/1/0/90)	**0.27**	**0.14, 0.38**	**6.29e-05**	**0.14, 0.38**	0	0.69
Negative rumination									
CERQ	3-Rumination	3	225 (9/1/0/90)	**0.41**	**0.24, 0.55**	**1.03e-05**	**0.14, 0.62**	43.7	0.14
Risk taking									
DERS	3-Impulse	5	463 (20/45/30/5)	**0.25**	**0.16, 0.34**	**4.34e-08**	**0.16, 0.34**	0	0.83
Adaptive emotion regulation strategies									
Acceptance									
CERQ	8-Acceptance	3	225 (9/1/0/90)	−0.03	−0.25, 0.20	0.80	−0.38, 0.33	59.0	0.08
DERS	1-Acceptance[a]	5	463 (20/45/30/5)	**−0.19**	**−0.31, −0.07**	**2.85e-03**	**−0.31, −0.07**	22.5	0.22
DERS	4-Awareness[a]	4	163 (56/10/21/13)	**−0.16**	**−0.31, −0.01**	**0.04**	**−0.31, −0.01**	0	0.45
DERS	6-Clarity[a]	5	463 (20/45/30/5)	**−0.19**	**−0.28, −0.10**	**4.84e-05**	**−0.28, −0.10**	0	0.94
Adaptive coping									
DERS	2-Goals[a]	5	463 (20/45/30/5)	**−0.26**	**−0.35, −0.16**	**5.65e-07**	**−0.35, −0.16**	7.5	0.29
DERS	5-Strategies[a]	5	463 (20/45/30/5)	**−0.26**	**−0.39, −0.12**	**3.62e-04**	**−0.39, −0.12**	37.3	0.19
Cognitive reframing									
CERQ	5-Putting into perspective	3	225 (9/1/0/90)	−0.04	−0.19, 0.09	0.55	−0.17, 0.09	0	0.86
CERQ	6-Positive refocus	4	376 (27/13/7/53)	−0.01	−0.13, 0.10	0.80	−0.16, 0.12	14.2	0.43
CERQ	7-Positive reappraisal	4	376 (27/13/7/53)	−0.07	−0.17, 0.03	0.18	−0.17, 0.03	0	0.68
CERQ	9-Focus on replanning	3	225 (9/1/0/90)	−0.07	−0.20, 0.06	0.27	−0.20, 0.06	0	0.94

Note: Results in bold are significant.

Abbreviations: BD, bipolar disorder; CERQ, Cognitive Emotion Regulation Questionnaire; CI, confidence intervals; D, depressive episodes; DERS, Difficulties in Emotion Regulation Scale; E, euthymic state; ED, emotion dysregulation; M, (hypo)manic episodes; NA, not available; PI, prediction intervals.

[a]The ES of these items have been inverted to present graphically coherent results, since the scale originally measures the individual's difficulties in adopting that emotion regulation dimension.

strategies, and mood psychopathology in patients diagnosed with BD. Overall, ED was significantly correlated to both depressive and (hypo)manic symptoms of BD. All maladaptive ER strategies included in the MA (i.e., negative focus, negative rumination, and risk-taking behaviors) were significantly and positively related to BD psychopathology. Looking at the correlations with the adaptive ER strategies considered, depressive symptoms were negatively correlated with all (i.e., acceptance, adaptive coping, and cognitive reframing), and (hypo)manic symptoms were negatively correlated with acceptance and adaptive coping. Statistical significance was not reached for the correlation between (hypo)manic symptoms and cognitive reframing.

ED, as measured by the total score of the Difficulties in Emotion Regulation Scale (DERS),[6] was significantly related to depressive symptoms with moderate effect size and no heterogeneity, and to (hypo)manic symptoms with weak effect size and moderate heterogeneity. The correlation between overall ED and depressive symptoms is consistent with previous findings in samples with MDD[11] and across different diagnoses.[7] At the same time, to the best of our knowledge, this is the first meta-analytic evidence of association with (hypo)manic symptoms. However, the proof of a real difference in the relationship between depressive and (hypo)manic symptomatology with ED seems to be scant. For example, there are only a few functional and structural neuroimaging studies on the topic and they have shown inconsistent results regarding the brain areas most involved in state-specific emotion processing.[18,69] For these reasons, it is possible that the differences in effect sizes between the two symptom polarities are a consequence of specific characteristics of the included studies rather than a real different correlation. The first point to consider in this regard is the inclusion of patients in the euthymic state. Previous studies showed that euthymic patients with BD show a higher prevalence of subthreshold depressive symptoms than subthreshold (hypo)manic symptoms.[70] The higher scores obtained by euthymic patients on scales assessing depressive symptoms rather than (hypo)manic symptoms could explain the stronger correlation between depressive symptoms and ED. Indeed, meta-regression analyses showed a significant decrease in the correlation between overall ED and (hypo)manic symptoms as the percentage of euthymic patients increased. Second, the nature of the instruments used to assess ED may play an important role. It is worth noting that the scale used in the considered studies (i.e., the DERS) predominantly measures negative ER, so people with an ongoing depressive episode or euthymic patients with prevalent depressive symptomatology may be more likely to score high, making the correlations stronger while individuals at risk of mania showed most problems on positive ER.[71,72] Confirming this hypothesis, meta-regression analyses showed that as the percentage of depressed patients and the mean scores of ED rating scales increase, the correlation between ED and (hypo)manic symptoms increases significantly. It is reasonable to speculate that assessment tools giving more relevance to positive emotion ER strategies would better capture the relationships between ED and (hypo)manic symptoms. In line with our results, only one preliminary study investigated differences in ED levels between patients in different mood states. It concluded that all patients with BD had alterations in ED, with no significant differences between groups.[73]

The absence of data from the included studies regarding the inclusion of patients experiencing mixed symptoms, as well as the absence of rating scales specifically designed to assess these symptoms, precluded any conclusive findings regarding the relationship between ED and this particular type of BD symptoms. Nevertheless, the metaregression analysis yielded a result indicating that as the proportion of patients with a depressive episode increases, the correlation between (hypo)manic symptoms and ED is also observed. This finding can potentially support the existence of a correlation between ED and mixed symptoms. Indeed, prior studies demonstrated a significant association between mixed symptoms, including insomnia, and ED.[74] The atypical or mixed features underlying a depressive episode may partly explain the difference in the magnitude of the observed correlation between depressive symptoms and (hypo)manic symptoms.

Regarding the details of the individual ER strategies, when considering maladaptive strategies, negative rumination, measured with the Cognitive Emotion Regulation Questionnaire (CERQ),[75] showed the strongest correlation with both BD symptoms polarities, with moderate effect sizes. Even when other scales are considered (i.e., the Ruminative Response Scale (RRS) and the Response Styles Questionnaire (RSQ)), the correlation remains significant, especially for depressive symptoms. Negative rumination is the tendency to respond to negative mood states with increased thoughts about negative attributes and negative life experiences.[3] Patients with BD are more likely to engage in negative and positive ruminative thoughts than healthy controls (HC).[13] A direct example of the relationship between rumination and BD symptoms comes from an RCT on a ER-focused therapy, which reported that a greater reduction in rumination during and after therapy predicts a greater response to depressive symptoms.[76] So far, rumination was proposed among the risk factors of (hypo)manic symptoms and mania onset.[72] We hypothesize that rumination is an ER strategy stably present in patients with

BD and stably related to BD symptomatology, which content may change depending on the symptom's polarity experienced. However, only one study[67] used ED rating scales that investigate positive rumination in the context of positive ER strategies (i.e., the Responses to Positive Affect questionnaire (RPA)[77]), and found no correlation between this type of rumination and BD symptoms. Positive rumination refers to the tendency to respond to positive affective states with recurrent thoughts about positive experiences.[78] In support of our hypothesis, positive rumination was statistically correlated to (hypo)manic symptoms,[79,80] higher mania lifetime frequency,[81] risk for (hypo)manic episodes,[82,83] and even to lower levels of depressive symptoms.[77,79] Evidence about rumination seems even more important considering that this strategy seems to play a decisive role in the development of dysregulated behavior.[84] Indeed, another positive and non-heterogeneous association was found for "risk-taking" strategy. The relation between BD and high-risk behaviors is well known.[13,30,85] The "impulse" subscale of the DERS and the "risk-taking" subscale of the RSQ explored this strategy, as the tendency to engage in risky (or impulsive, reckless) behaviors in response to depressed mood.[3] The correlations were moderate with depressive and weak with (hypo)manic symptoms, probably because these items explore the regulation of negative emotions, as mentioned earlier. Risk behaviors are in fact a core symptom of mania[39] and, importantly, they are also related to aggressive behaviors,[86] mediated by common factors such as affective temperaments[87,88] or childhood maltreatment.[89,90] Indeed there is evidence that risk-taking was dependent on current mood status, as scores were highest in people with BD who were currently manic compared to those who were currently depressed or euthymic.[91,92]

Negative focus strategy, defined as over-emphasizing the negative aspects of an experience and predicting the worst possible outcome, and focusing on self-critical thoughts, blaming self or others for events/situations that are not the complete responsibility of the individual,[3] also appeared to be correlated positively with both polarities of BD. Patients with BD were generally more likely to anticipate possible catastrophic situations or blame themselves or others as coping strategies to negative events in comparison with HC.[13] More in detail, this strategy was studied through the CERQ subscales "catastrophizing," "self-blame," and "blaming others." The "self-blame" subscale is the only one correlated with both polarities, with no heterogeneity. Consistently, self-blame is a core symptom of depression.[93] In addition, BD severely impacts the lives of patients and their families, often resulting in feelings of guilt, shame, or remorse for things that happened during an acute, predominantly manic, episode,[94] encouraging a strong self-critical attitude, which may come to be a trait.[95] The same attitude could explain the non-heterogeneous association between "catastrophizing" and (hypo)manic symptomatology, and the significant association with depressive symptoms resulting by removing the study by Green et al. Furthermore, (hypo)manic symptomatology is most associated with increased self-esteem and grandiose thoughts about oneself,[39,96] which could explain the association with blaming others that is only present in this symptom dimension.

The picture changes when considering the results of adaptive ER strategies, where pooled correlations are negative with both depressive and (hypo)manic symptoms.

The "acceptance" strategy refers to accepting and resigning oneself to the emotion being experienced.[3] The "non-acceptance" subscales of the DERS and "acceptance" subscales of the CERQ measure two different attitudes, with the former aimed at measuring the degree of non-acceptance of one's negative emotions,[6] and the latter measuring the degree of acceptance of emotions as a coping strategy.[75] When we considered "non-acceptance" of negative emotions as defined by DERS, a significant negative correlation was found for both polarities without heterogeneity, even if publication bias was detected for the association with depressive symptoms. When "acceptance" was considered as a coping strategy as defined by the CERQ, no significant association was found for either depressive or (hypo)manic symptoms in the main analysis. However, after removing the study by Wolkenstein et al., a positive significant association was found between increasing depressive symptoms and an increase in "acceptance" of emotions. This association was positively influenced by age, percentage of patients diagnosed with BD-I, and mean scores of the depressive symptoms' scales. It is interesting to note that the study by Wolkenstein et al. included patients of lower age, a low percentage of patients diagnosed with BD-I, and mean scores of the depressive symptoms' scales that were almost half of those in other studies, which may explain the lack of significant association in the main analysis. Considering the other subscales of the DERS, "awareness" reflects the tendency to attend to and acknowledge emotions, while "clarity" the extent to which individuals know the emotions they are experiencing.[6] The first strategy was correlated only to (hypo)manic symptoms, while the second to both polarities. During the experience of both depressive and (hypo)manic symptoms, there is a decreased tendency to recognize and accept emotions, confirming previous evidence demonstrating impaired mentalizing ability (theory of mind), in acute episodes of BD.[97]

"Adaptive coping" defined as the tendency to engage in emotion regulation behaviors that are adaptive, comprising distraction and problem-solving,[3] reached statistical significance for and was negatively correlated to both polarities. This dimension was studied by the two subscales of the DERS "goals" and "strategies," which reflect the difficulties in concentrating and accomplishing tasks when experiencing negative emotions, and the belief that there is little that can be done to regulate emotions effectively once an individual is upset.[6] It is possible that when the BD symptomatology increases, the interference of mood and cognitive impairments[98] may affect the use of adaptive strategies. In addition, the dimension we have seen to be most associated with symptoms, rumination, in turn interferes with concentration, problem-solving, and the performance of goal-directed activities.[84]

Finally, for "cognitive reframing" we found negative significant associations only for depressive symptomatology. This strategy refers to interpreting an event or experience in a way that adaptively alters a person's emotional response in a positive way.[3] It was explored by four CERQ subscales, "putting into perspective," "positive refocusing," "positive reappraisal," and "refocus on planning," and all these subscales appeared to be correlated with symptoms, except for "positive refocus," which was correlated with depressive symptoms only after the study by Green et al. was removed. The effect sizes of "positive reappraisal" and "refocus on planning" resulted moderate. The first refers to thoughts of attaching a positive meaning to the event in terms of personal growth, and the second to thinking about what steps to take and how to handle the negative event.[75] The correlations observed may be due to the combined influence of cognitive deficits in BD[98] and the tendency of individuals with bipolar depression to create more negative interpretations and fewer positive meanings when processing information.[99]

4.1 | Limitations

This is the first SR to describe the relationship between ED and BD psychopathology. Together with our two previous SRs,[13,14] it represents a primer in understanding the ED construct in BD, which has previously received little attention. Enhanced knowledge in this area may identify specific treatments that can optimize ED outcomes according to personalized medicine and promote recovery by aiding the development of new transdiagnostic treatments.[36] As suggested for mood instability,[100] assessment of ED in clinical trials may be more valuable than conventional outcomes in estimating disease severity or patients' functioning. However, there are limitations to our study. First, the likelihood of identifying heterogeneity and predictors with meta-regressions was reduced by the paucity of includable primary studies, and analyses of their magnitude were limited.[50] Second, the effect sizes found in our analyses were generally weak or moderate at best, suggesting that some of the significant results found in this review may be influenced by sample size bias.[101] Third, correlation is not a suitable measure for drawing conclusions about the directionality and causality of the described associations.[102] Fourth, only one included study was longitudinal, while the others were cross-sectional, so the direction of causality remains unclear and should be examined in future prospective studies.[103] Fifth, the studies included in the analysis primarily comprised heterogeneous populations of patients, including those in euthymic states, with depressive and (hypo)manic episodes. In some cases, the studies solely involved euthymic patients. To gain a more comprehensive understanding of the phenomenon across different phases of the disorder, it is recommended that future studies concentrate on investigating more homogeneous patient populations. This approach would enable a more precise characterization of the phenomenon within specific phases of the disorder. Sixth, it was not possible to control the results for clinically relevant patterns such as rapid-cycling,[104] atypical and mixed features of depression,[74] lifetime treatment response (including harm) to antidepressants, atypical antipsychotics[105] or lithium,[106] post-partum,[107] seasonal features,[108] functioning,[109] comorbid eating disorders,[110] borderline personality disorder[111] or substance use disorders[112] as such features may be either relatively frequent among people with BD and likely represent the expression of ED themselves or being modulated (and modulators) of ED anyway. Finally, most of the patients in those studies were on medication, which may influence the findings.[113]

To Conclude, ED is a transdiagnostic construct that is present in patients with BD and correlates significantly with its symptomatology. The present study points out that it mainly occurs during mood alteration. Both depressive and (hypo)manic symptoms were associated with ED in BD. However, the association with depressive symptoms was stronger and more stable than with (hypo)manic symptoms. In understanding BD, our results may be useful in outlining those particularly relevant features to assist the development of novel, transdiagnostic, both psychotherapeutic and pharmacological[36] treatments for those patients having higher ER-related impairments. However, studies including patients with mood episodes and longitudinal design are needed to provide more robust evidence and explore the causal direction of these associations. In addition, psychiatric diagnosis and psychopathological symptoms are not the only elements that

should be considered when approaching ED. Future studies should primarily focus on the complex interactions between cognitive, social, and cultural aspects, as well as biological correlates, to improve knowledge on a topic that is still understudied.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Lydia Fortea https://orcid.org/0000-0001-6778-2316
Gerard Anmella https://orcid.org/0000-0002-6798-4054
Alessandro Serretti https://orcid.org/0000-0003-4363-3759
Eduard Vieta https://orcid.org/0000-0002-0548-0053

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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