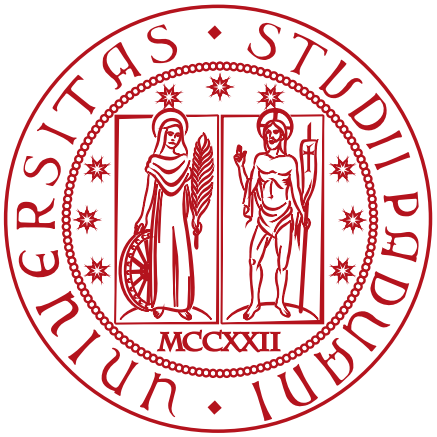

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Clinical correlates of emotional dysregulation in bipolar disorder spectrum: a case-control study

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ABSTRACT

Background:

Differentiating bipolar disorder (BD) from borderline personality disorder (BPD) can be challenging considering shared common factors, including emotional dysregulation. Although alterations in emotional regulation are a key feature of both these diseases, our clinical study investigates possible differences in emotional dysregulation between patients with BD and BPD, as well as possible differences in childhood trauma, impulsivity and daily functioning scores.

Material and methods:

Inclusion criteria were: inpatients diagnosed with BD or BPD, as confirmed by the Structured Clinical Interview for DSM-V-Patient Edition (SCID-I and SCID-II).

Each participant underwent psychometric rating scales exploring emotional dysregulation using the Difficulties in Emotion Regulation Scale (DERS), impulsivity through the Barratt Impulsiveness Scale (BIS-11), history of childhood trauma with the Childhood Trauma Questionnaire (CTQ), and global functioning using the WHO Disability Assessment Schedule (WHODAS-2). For the analysis of socio-demographic and clinical data among diagnostic groups, we used $\chi 2$-tests for categorical variables and one-way ANOVA for continuous data, with pairwise $\chi 2$ /Tukey post hoc comparisons in case of statistical significance. We compared psychometric ratings between BD, BPD, and HC using ANOVA tests, followed by Tukey's post hoc analysis in case of statistical significance.

Results:

Forty-two patients with BD, 32 subjects diagnosed with BPD, and 62 healthy controls (HC) were recruited.

Compared to HC, patients with BD showed significantly higher values in DERS, CTQ, and WHODAS.2 total scores, while they did not differ significantly from HCs in BIS-11 total scores. Compared to those with BPD, patients with BD presented significantly lower scores in DERS, BIS-11, and WHODAS.2 total scores, while the difference was not significant in the CTQ total score. On the other side, patients with BPD exhibited significantly higher DERS, BIS-11, CTQ and WHODAS.2 total scores compared to HCs.

Patients with BD displayed significant higher values in DERS subscales compared to HCs, except for “DERS difficulties engaging in goal-directed behavior”, “awareness”, and “clarity” subscales. Also, patients with BD had lower ratings than those with BPD in DERS subscales, except for “DERS difficulties engaging in goal-directed behavior” and “awareness” which did not show significant differences between patients’ subgroups. Patients with BPD had significant higher values in DERS subcategories compared to HCs, except for “DERS awareness”, where the difference was not significant.

In the BIS-11 score, patients with BD did not differ significantly from controls in any subcategory, while they exhibited significantly lower values in all subdomains

of BIS-11, except for "BIS-11 motor impulsivity" and "BIS-11 not planned impulsivity" when compared with BPD patients.

Both patients with BD and BPD displayed significantly higher ratings in all CTQ subscales compared to HCs, with the exception of “CTQ scale minimization”, where the difference between patients and HC was not significant. Comparing patients with BD and those with BPD, no significant differences were found in any subcategories between the two groups.

Finally, both patients with BD and BPD presented significantly higher scores in all subscales of WHODAS.2 compared to HCs. Conversely, patients with BD displayed lower values in both WHODAS TOTAL and all subcategories compared with those with BPD, except for "WHODAS.2 life activities” and “WHODAS.2 participation”.

Conclusion:

In conclusion, the current study confirmed that both patients with BD and BPD exhibited difficulties in emotion regulation compared to controls.

These results also propose that, compared to BPDs, individuals with BD display better emotion regulation strategies and less frequently resort to attitudes of non-acceptance, in addition to possessing an increased emotional clarity. Furthermore, patients with BD displayed less difficulty managing impulsive behaviors than those with BPD. Although patients with BD did not show increased impulsivity compared to HC, probably due to the relatively small sample size, patients with BD recurred to less impulsive behavior than those with BPDs, with two exceptions. In fact, both BD and BPD patients seemed to resort to the same level of unplanned impulsivity and motor impulsiveness.

The presence of childhood abuse, on the other side, was high in both groups of patients compared to controls but did not differ significantly from each other’s. The only attitude used equally, both in patients and healthy controls, was the propensity to minimize or deny their traumatic experiences.

Finally, the level of dysfunction in daily activities appeared to differ between groups, with patients with BD showing intermediate daily functioning compared to those with BPD and HCs.

The current findings may improve the differential diagnosis of these disorders and inform the development of tailored interventions for BD and BPD. Future studies with longitudinal design and larger samples are needed to confirm our preliminary findings and to help establish causality in the results.

ABSTRACT

Introduzione

Differenziare il disturbo bipolare (BD) dal disturbo borderline di personalità (BPD) può essere difficile considerando fattori comuni condivisi, tra cui la disregolazione emotiva. Sebbene le alterazioni nella regolazione emotiva siano una caratteristica chiave di entrambe queste malattie, il nostro studio clinico indaga possibili differenze nella disregolazione emotiva tra i pazienti con BD e BPD, così come possibili differenze nel trauma infantile, impulsività e punteggi di funzionamento quotidiano.

Materiali e metodi

I criteri di inclusione sono stati: pazienti ricoverati con diagnosi di BD o BPD, come confermato dall'intervista clinica strutturata per DSM-V-Patient Edition (SCID-I e SCID-II). Ogni partecipante è stato sottoposto a scale di valutazione psicometrica che esplorano la disregolazione emotiva utilizzando la scala di regolazione delle difficoltà emotive (DERS), l'impulsività attraverso la scala di impulsività di Barratt (BIS-11), la storia del trauma infantile con il questionario sul trauma infantile (CTQ) e il funzionamento globale utilizzando il programma di valutazione della disabilità dell'OMS (WHODAS-2). Per l'analisi dei dati socio-demografici e clinici tra i gruppi diagnostici, abbiamo utilizzato χ2-test per le variabili categoriche e unidirezionali ANOVA per i dati continui, con confronti post hoc a coppie χ2 /Tukey in caso di

rilevanza statistica. Abbiamo confrontato le valutazioni psicometriche tra BD, BPD e HC in caso di differenze significative.

Risultati

Quarantadue pazienti con BD, 32 soggetti con diagnosi di BPD e 62 controlli sani (HC) sono stati reclutati.

Rispetto all'HC, i pazienti con BD hanno mostrato valori significativamente più alti nei punteggi totali di DERS, CTQ e WHODAS.2, mentre non differiscono significativamente dagli HC nei punteggi totali di BIS-11. Rispetto a quelli con BPD, i pazienti con BD presentavano punteggi significativamente più bassi nei punteggi totali DERS, BIS-11 e WHODAS.2, mentre la differenza non era significativa nel punteggio totale CTQ. Dall'altro lato, i pazienti con DBP hanno mostrato punteggi totali significativamente più alti di DERS, BIS-11, CTQ e WHODAS.2 rispetto agli HC. I pazienti con BD hanno mostrato valori significativamente più alti nelle sottoscale DERS rispetto agli HC, ad eccezione delle sottoscale "difficoltà DERS di impegnarsi in comportamenti orientati agli obiettivi", "consapevolezza" e "chiarezza".

Inoltre, i pazienti con BD hanno avuto valutazioni più basse rispetto a quelli con BPD nelle sottoclassi DERS, ad eccezione delle "difficoltà DERS che si impegnano in un comportamento diretto" e "consapevolezza" che non mostrano differenze significative tra i sottogruppi dei pazienti. I pazienti con BPD avevano valori significativamente più alti nelle sottocategorie DERS rispetto agli HC, ad eccezione della "consapevolezza DERS", dove la differenza non era significativa. Nel punteggio BIS-11, i pazienti con BD non differivano significativamente dai controlli in nessuna sottocategoria, mentre mostravano valori significativamente più bassi in tutti i sottodomini di BIS-11, ad eccezione di "impulsività motoria BIS-11" e "impulsività non pianificata BIS-11" rispetto ai pazienti con BPD. Entrambi i pazienti con BD e BPD hanno mostrato valutazioni significativamente più elevate in tutte le sottoscale CTQ rispetto agli HC, con l'eccezione della "minimizzazione della scala CTQ", dove la differenza tra i pazienti e HC non era significativa. Confrontando i pazienti con BD e quelli con BPD, non sono state trovate differenze significative in nessuna sottocategoria tra i due gruppi. Infine, entrambi i pazienti con BD e BPD hanno presentato punteggi

significativamente più alti in tutte le sottoclassi di WHODAS.2 rispetto agli HC. Al contrario, i pazienti con BD hanno mostrato valori più bassi sia in WHODAS TOTAL che in tutte le sottocategorie rispetto a quelli con BPD, ad eccezione di "WHODAS.2 life activities" e "WHODAS.2 participation".

Conclusioni

In conclusione, lo studio attuale ha confermato che entrambi i pazienti con BD e BPD hanno mostrato difficoltà nella regolazione delle emozioni rispetto ai controlli.

Questi risultati propongono anche che, rispetto ai PBD, gli individui con BD mostrano migliori strategie di regolazione delle emozioni e meno frequentemente ricorrono ad atteggiamenti di non accettazione, oltre a possedere una maggiore chiarezza emotiva. Inoltre, i pazienti con BD hanno mostrato meno difficoltà a gestire comportamenti impulsivi rispetto a quelli con BPD. Anche se i pazienti con BD non hanno mostrato un aumento dell'impulsività rispetto all'HC, probabilmente a causa della dimensione del campione relativamente piccola, i pazienti con BD ricorrevano a un comportamento meno impulsivo rispetto a quelli con BPD, con due eccezioni. Infatti, sia i pazienti BD che BPD sembravano ricorrere allo stesso livello di impulsività non pianificata e impulsività motoria.

La presenza di abusi infantili, d'altra parte, era alta in entrambi i gruppi di pazienti rispetto ai controlli, ma non differiva significativamente l'uno dall'altro. L'unico atteggiamento usato ugualmente, sia nei pazienti che nei controlli sani, era la propensione a minimizzare o negare le loro esperienze traumatiche.

Infine, il livello di disfunzione nelle attività quotidiane è sembrato differire fra i gruppi, con i pazienti con BD che mostravano il funzionamento quotidiano intermedio confrontato a quelli con BPD ed HC.

I risultati attuali possono migliorare la diagnosi differenziale di questi disturbi e informare lo sviluppo di interventi su misura per BD e BPD. Sono necessari studi futuri con progettazione longitudinale e campioni più grandi per confermare i nostri risultati preliminari e per aiutare a stabilire la causalità nei risultati.

CHAPTER 1 BIPOLAR DISORDER

1.1 INTRODUCTION

The term bipolar disorder (BD) refers to a pathology that is included in the group of mood disorders. Within this group, BD is distinguished by the presence of recurrent episodes of mania and/or hypomania, which may or may not be accompanied by severe depressive episodes. [36]

BD is a complex pathology characterized by severe mood changes, neuropsychological deficits, immunological and physiological changes, and functioning changes[195].

The diagnosis of BD is frequently difficult, owing in part to the overlapping clinical characteristics of this pathology with those of other disorders; nonetheless, early recognition of the pathology is essential, as recovery rates are higher in patients with a shortened disease duration. [195]

The high prevalence of comorbidity with other psychiatric pathologies further complicates the clinical picture[36]: comorbidity in BD is associated with earlier exordium of disease, more complex clinical presentation, higher suicide rates, and poorer response to treatment [155].

Bipolar disorder is divided into five categories: bipolar disorder type I, type II, cyclothymic, "induced by medical or pharmacological conditions," and "not otherwise specified." Most patients meet the criteria of the first three types.

More specifically, bipolar type I disorder (BD-I), is characterized by the occurrence of at least one episode of mania[155]; while bipolar type II disorder (BD-II), is associated by coexistence of an episode of hypomania and an episode of major depression[155]; and cyclothymic disorder, with recurrent depressive and hypomanic states not defined as major episodes.

1.2 Epidemiology

According to epidemiological research, the lifetime prevalence of bipolar type I is approximately 1% in the general population. [22] [185] According to a significant

cross-sectional study of 11 countries, the lifetime prevalence of bipolar spectrum disorders was 2.4%, with bipolar type I at 0.6% and bipolar type II at 0.4%. [157] Although findings varied across countries, this indicated a lower prevalence of bipolar type I and II than previous studies[185] [237], while the prevalence of bipolar type I in the United States was found to be 1%, slightly higher than the other countries. It is unclear whether the discrepancies were attributable to the more stringent diagnostic criteria utilized in this study or to genuine disparities in bipolar prevalence rates between nations and ethnic groups. In one of the very few epidemiological studies conducted in England, the Adult Psychiatric Morbidity Survey 2014 reported a 2% lifetime prevalence of probable bipolar. Although the method of measurement suggests that this is an underestimate, the study did not differentiate between subtypes of bipolar disorder. [238] Although the majority of included studies were from North or South America, a recent meta-analysis of 25 studies found a pooled lifetime prevalence of 1.06 percent and 1.57 percent for bipolar type I and II, respectively[40]. However, a similar prevalence has been found in the United Kingdom, Germany, and Italy[68], and a systematic review of African studies found a lifetime prevalence ranging from 0.1 to 1.83 percent[63].

Ethnicity

The cause of worldwide differences in the frequency of bipolar disorder is unclear, although Ethnicity[223], cultural factors[106], and modifications in diagnostic criteria and study methodology[106] may all contribute to the variable worldwide prevalence of bipolar disorder. The evidence for variable incidence of bipolar disorder in different ethnic groups is mixed, with some research suggesting greater prevalence in Caucasians [148, 239] and others in nonwhite communities[240]. A comprehensive analysis revealed no substantial evidence for ethnic inequalities and emphasized that individual research inconsistencies may be attributable to cultural characteristics, migration, and higher rates of misdiagnosis of schizophrenia as opposed to bipolar disorder among black ethnic groups[223].

Gender

Certain studies have found a gender-equal distribution of bipolar[223], while others have found a greater incidence of manic episodes and bipolar type I in males and bipolar type II in females[157]. According to the available information, bipolar disorder seems to be rather evenly distributed throughout sexes and races.

Age

Based on research spanning 20 to 30 years**[185]**, the average age of onset for bipolar illness appears to be early twenties**[157]**. Validating the bimodal distribution theory for the prevalence of bipolar disease, a large population-based cohort study revealed two peaks in age of onset at 15–24 years and 45–54 years**[241]**. Due to the long periods of untreated illness, when symptoms can be nascent or apparent without individuals accessing services, which is frequently used as the measure of onset in many studies, age of onset estimates for bipolar are difficult to define precisely**[108]**. Additionally, there appear to be differences in the presentation and clinical course of bipolar disorder based on age of onset**[125]**, with later-onset mania having higher rates of psychiatric and medical comorbidities such as suicidality and vascular disease**[242]**.

Sociodemographic factors

Numerous studies have examined the relationship between the prevalence of bipolar disorder in relation to sociodemographic factors, but the results have been inconsistent[223].

There is evidence of elevated rates among low-income, unemployed, and unmarried groups[223], although the social upheaval produced by severe mental illness cannot be ruled out as a cause[22]. In contrast, higher socioeconomic status, higher career status, and creativity are related with a higher incidence of bipolar disorder [22, 243–245], which is the reverse of unipolar depression and

schizophrenia[22]. However, these studies are limited by their small sample sizes and lack of consistency[246]. Some hypotheses implicate a referral bias favoring individuals with a higher socioeconomic status, while others suggest that those with high-functioning creative talents may be genetically predisposed to bipolar disorder[22].

There is accumulating evidence correlating urban environments with a higher incidence of bipolar disorder[223]. Although the evidence for schizophrenia is more solid and there are various plausible explanations[247], the link between urbanization and bipolar disorder is not as evident. In contrast, a cohort study found a substantial correlation between urban living and the incidence of psychotic bipolar disorder, but none for bipolar disorder without psychosis[248]. This may suggest that urban living is a transdiagnostic risk factor for psychotic disease, as opposed to bipolar disorder.

Mortality and quality of life

This study emphasizes the increased risk of mortality from any cause among BPAD patients. Summary SMR estimates derived from a meta-analysis of random effects demonstrated that the overall mortality rate in BPAD is double that of the general population. These natural causes of death include an almost doubled likelihood of cardiovascular illness (heart attacks, strokes, etc.) and a triple likelihood of respiratory disease (COPD, asthma). Unnatural deaths are about seven times more frequent due to a 14-fold increase in the probability of suicide and a roughly four-fold increase in the likelihood of other violent fatalities (accidents, homicide, etc.). Especially troubling is the lack of a correlation between mid-decade cohort follow-up and SMR: having BPAD in the 2000s had the same risk of death as in the 1950s. This disparity in medical illness deaths may widen if it is not directly addressed due to the increased use of second-generation antipsychotics in these cohort [249]-[250] and the associated increased risk of cardiovascular disease, the failure of smoking cessation policy to address the needs of the severely mentally ill relative to the general population [251] [252], and the ongoing lack of equality in access to health

care for people with bipolar disorder[251]. Special attention must be paid to concurrent substance abuse, the risk of coercion, exploitation, receiving and perpetrating violence, and suicidal thoughts in order to reduce the likelihood of unnatural deaths.[251]-[253].

Unless this disparity in medical sickness mortality is addressed, it is likely to worsen. In order to reduce the increasing prevalence of unnatural deaths, special attention must be made to comorbid drug abuse, the danger of coercion, exploitation, the receipt and perpetration of violence, and suicide thoughts.[254]; However, it is possible that there are even more regional differences in BPAD outcomes. This meta-analysis reveals that mortality estimates for BPAD are not uniform throughout the United States or Europe. Despite the increased accuracy in SMR estimates that larger studies should provide, adjusting for cohort size did little to reduce heterogeneity. Stratifying by decade of data collection had little effect on heterogeneity, indicating that the discrepancies are not due to therapeutic advancements over time. Studies of inpatient populations and community cohorts were likewise diverse, indicating that these disparities are not due to treatment utilization or disease severity.

The research considered in this study have many limitations. SMRs were frequently simply age and gender adjusted; hence, additional research population features, such as disease duration and lifestyle factors, may have contributed to the substantial variation. For example, it was unable to determine whether present or previous smoking led to increased respiratory mortality. Because disease severity was not assessed in all the included studies, there is no way to assess heterogeneity in overall mortality by severity. It has been shown that people with bipolar illness amass a variety of medical risk factors, including smoking, use of alcohol and other illegal substances, prescription medication, and concomitant anxiety and eating disorders, all of which contribute to an earlier disease start, Poor health-care involvement and long-term consequences [255]. These risk variables can be allocated in a variety of ways, both geographically and chronologically. Many of the included studies obtained the cause of death from

death certificates, which may have resulted in misclassification bias. A mental health diagnosis has been demonstrated to enhance the likelihood of a coroner's conclusion of suicide rather than accidental or unknown death [192], but it may also lower identification of terminal disease, resulting in miscoding of physical cause of death[251].

This meta-analysis reveals differences in mortality between BPAD patients and the general population. Patients with BPAD have more than twice the all-cause mortality [256] as those with schizophrenia. The death rate from all physical illnesses and unnatural causes is increasing. The variation in all-cause mortality is significant across time and place. There is no indication that all-cause mortality among BPAD patients has decreased over time in comparison to the general population. (10)

Medical comorbidity

Bipolar disorder has been linked to a range of medical and psychiatric conditions (10) (11) [257]. Several hypotheses exist for this, including shared genetic and environmental vulnerabilities, treatment outcomes, clinician recognition bias, and the possibility of a direct causal link in either direction.

A new large meta-analysis of retrospective cohort studies uncovered considerable evidence of an association between bipolar disorder and irritable bowel syndrome (IBS).[258]

However, potential confounding variables such as antidepressant use were not considered. Furthermore, there is evidence that both diseases may have an inflammatory [259] [260] [29]and stress-related [261] [130]causes, which could explain the link.

In recent meta-analyses, asthma, obesity, migraines (18), and head injuries [262] have all been associated to bipolar disorder. The evidence for these connections is limited due to the small number of studies examined, the majority of which were cross-sectional and lacked data to account for confounding variables. Nonetheless, a retrospective cohort [263]and a large prospective [264] research support the association, which may be mediated by shared inflammatory pathways [259] [260]or the use of corticosteroids in infancy [257] [263]. Medication and lifestyle variables significantly complicate the obesity correlation, for which there are few prospective studies and scant evidence of a causal relationship, whilst the association with traumatic brain injury may be confounded by 'accident propensity' or physical abuse[265]. There are indications that bipolar disorder is more prevalent among sufferers.

A meta-analysis revealed that bipolar patients had a high lifetime prevalence of anxiety disorders [167] and that ADHD, conduct disorders, anger, and impulsivity appeared to increase the likelihood of developing bipolar illness[67].

Autoimmune diseases and DB

Autoimmune disorders are defined by an immune malfunction that prevents the body from recognizing and responding to host tissues. Numerous epidemiological studies have found increased rates of BD in patients with various autoimmune diseases: a diagnosis of Guillain-Barré syndrome, chronic inflammatory bowel disease (Chron or Rettocolite Ulcerosa), autoimmune hepatitis, multiple sclerosis, or rheumatoid arthritis was associated with an increased relative risk of BD[58].

The HPA axis is the main mediator of the biological response of the organism to stress[274], and its alteration is considered a relevant factor in the clinical course of BD, since it could help to increase the risk of relapse of BD resulting in intense psychological stress.[45] Patients with BD showed more intense HPA axis activity compared to healthy controls, witnessed by higher basal levels of cortisol and more intense response to the stimulus test with CRH, with more evident hyperactivity in the manic phase.[25] With the progression of BD, It is also considered that alterations of the HPA axis play a role in reducing stress resistance and increasing the risk of new disease episodes.[76] Abnormalities of this system also increase the risk of cognitive dysfunctions[140], in addition to having a neurotoxic effect on the hippocampus[141].

Cardiovascular disease, endocrine dysfunction and BD

Immune dysfunction, characterized as the presence of low-grade chronic inflammation, has been demonstrated to play a significant role in the etiopathogenesis of cardiovascular illnesses, obesity, and insulin resistance, with elevated levels of pro-inflammatory cytokines measured in all three situations [266]. Cardiovascular illness has long been recognized as a significant comorbidity of BD; the risk of death from cardiovascular disease in BD patients is 2,3 times that of the general population[137]. In terms of temporal examination, BD is frequently diagnosed at a young age, whereas cardiovascular pathologies manifest at a later age: the temporal relationship between the two entities may suggest that elevated levels of inflammation associated with BD lead to the development of cardiovascular disease over time[193] [267].

Type 2 diabetes mellitus and obesity are two other diseases that have a high prevalence in patients with BD, with a value 2 to 4 times higher than that of the general population[137] [267]; additionally, patients with BD and obesity have a poorer prognosis, more frequent recurrences of depressive episodes, increased cognitive dysfunction, and an increased risk of suicide[137].

Moreover, the pro-inflammatory state raises the activity of the hypothalamic-pituitary-adrenal axis, resulting in hypercortisolemia, which increases the risk of

insulin resistance, obesity, and humoral and cognitive changes[267]. Immunological dysfunction may consequently cause and sustain both BD and medical comorbidities, creating a two-way interaction that promotes immune dysfunction[193].

In this way, immunological dysfunction can serve as a novel therapeutic target in the quest for new medications for the treatment of BD[193]; however, studies on anti-inflammatory and immunomodulatory therapies have not yet demonstrated their efficacy to support their usage in the treatment of BD.

Suicide

BD has one of the highest suicide rates among psychiatric pathologies, and carries with it a risk approximately 20-30 times higher than that of the general population[161]: it is estimated that 30-50% of adults with BD attempt suicide at least once in their lives, and that about 15-20% die of suicide[82]. Patients with BD and previous suicide attempts also have a lower quality of life than patients with BD but no suicide attempts[1].

Also, suicide attempts in the patient with BD present a much higher lethality than in any other psychiatric pathology and in the general population. The risk of suicide in BD is variable depending on the characteristics and stage of the disease: suicide attempts are more frequently associated with depressive or mixed episodes of disease, and therefore the determination of the predominant disease polarity may be useful in predicting the risk of suicide[268].

Risk factors for suicide typical of the general population (male, living alone, divorce, childlessness, Caucasian ethnicity, age <35 or >75, unemployment)[198] are also valid for suicide in BD, which however presents specific: a previous suicide attempt, the presence of suicidal ideations, the presence of positive family history for attempted or completed suicides, the presence of BD in rapid cycles, the presence of an episode of depression and an early age of onset of disease are all elements that need to be thoroughly analyzed in the stratification of suicide risk in the patient with BD .

Although tools are available that can help clinicians identify patients at high risk of suicide [such as the Columbia Suicide Severity Rating Scale (C-SSRS), the Columbia Classification Algorithm of Suicide Assessment (C-CASA), or the Tool for Assessment of Suicide Risk (TASR)], there are none specifically validated for the patient with BD; also the search for clinical markers, genetic or neuroimaging that can be used in BD patients for the assessment of suicide risk has so far not returned significant results[161].

As for the management of the patient with BD and suicide risk, lithium has a reduction effect of suicide attempted and completed in the patient with unipolar or bipolar depression, but it is a prophylactic agent, not usable in acute[198]: faster treatment of suicide is possible by intravenous or intranasal administration of ketamine[232]. Electroconvulsive therapy (ECT) has also been shown to be better as an anti-suicidal agent than pharmacological treatment[269], and was also proposed as a treatment of choice in emergency situations for patients at high risk of suicide[270].

1.3 ETIOLOGY AND PATHOGENESIS IN BIPOLAR DISORDER [165]

Switch process in bipolar disorder

Every BD patient exhibits evidence of manic and depressed symptoms to varied degrees, and diverse pathophysiological processes are believed to cause these affective alterations. Some individuals experience fast changes in symptomatology that last for days or weeks, while others with more severe instances have simultaneous manic and depressed symptoms that alternate every few hours, a phenotype known as ultra-rapid cycling bipolar disorder[19]. The processes underpinning switching between states must be uncovered for successful therapies, and this element is appropriately considered as the "holy grail of BD research." Important insights have been gained in this regard by investigating the

switch process caused by pharmacotherapeutic and chronobiological measures used in the treatment of mood disorders[231].

Circadian dysregulation hypothesis of mood disorders

Mood disorders are characterized by disturbances in the sleep-wake cycle, alterations in daily activity levels, and irregular mealtimes, all of which indicate a significant issue with the circadian rhythm[211]. Research has gradually uncovered the etiopathological mechanisms underlying this relationship during the past few decades[24]. It is now evident that circadian rhythm instability is the primary cause of mood disorders.

The deterioration of mood in people with bipolar disorder has been shown to be caused by seasonal fluctuations in light intensity[271]. Additionally, bipolar patients have disturbances in important biological processes regulated by the circadian rhythm, including sleep, diurnal activity, hormone levels, and body temperature[272]. Mood stabilizers such as lithium work to restore some of these disturbed rhythms by causing a significant phase delay in daily oscillations and increasing rhythmic amplitude, which may be the key to their therapeutic benefits[164]. Thanks to the discovery and replication of the genes that comprise the molecular clock, it is now possible to investigate the molecular mechanisms underlying the relationship between the circadian system and mood disorders. A brief description of the molecular clock is provided to clarify the subcellular mechanisms that characterize the daily rhythmic oscillations of mammalian species.

The molecular clock

In the absence of external environmental signals, the primary molecular clock resides in the supraschiasmatic nucleus (SCN) of the hypothalamus and consists of an oscillating transcription-translation circuit that lasts around 24 hours. BMAL1 is a dimer comprising the Brain and Muscle ARNT-like Protein 1 and Circadian

Locomotor Output Cycles Kaput (CLOCK) proteins are the primary transcription activators. This molecule binds to Enhancer-box regions in the promoters of many genes, including Period (Per) and Cryptochrome (Cry). The PER and CRY proteins are translated in the cytoplasm and phosphorylated by casein kinase 1 before being targeted by glycogen synthase kinase 3, altering their survival, relationship, and nucleocytoplasmic transport capability. When these bind to DNA, a negative feedback loop is created that inhibits their activity Clock/Bmal1 activity. In addition, CLOCK/BMAL1 induce the transcription of orphan nuclear receptor genes Rev-erb and Ror, which, inhibit and stimulate, respectively, the transcription of Bmal1 and Clock. Numerous regulatory kinases, phosphatases, and secondary feedback loops work on the molecular clock, which further complicates the circadian process, as previously mentioned[273].

Hypothalamic-pituitary-adrenal axis (HPA)

Alterations in neurotransmission

The monoaminergic hypothesis states that an alteration of serotoninergic, noradrenergic, and dopaminergic transmission in the central nervous system is causally related to the development of clinical features of depression or mania typical of BD [275]. This is supported by the observation in the brains of individuals with BD of a higher presence of MAO-A and a lower presence of 5-HT during a depressive episode. Changes in cholinergic and glutamatergic transmission may also been implicated[276, 277].

Neuroplasticity and neurotrophic signaling changes

Numerous preclinical and clinical studies have shown that there are significant decreases in the levels of neurotrophic factors (specifically BDNF and its TrkB receptor) in the blood and brain of patients with BD[278]; these alterations are thought to play a causal role in the context of neuroprogression, a pathological cerebral remodeling that in a substantial proportion of patients with BD appears to be associated with their progressive cognitive deterioration.

Mitochondrial dysfunction

Mitochondria play a fundamental role in the modulation of neuronal activity and plasticity and behavioral adaptations, acting primarily on long-term potentiation, a fundamental process in learning and memory.[219] Analysis post-mortem of the prefrontal cortex of patients with BD revealed morphological abnormalities and altered aggregations of mitochondria[37]: this finding, along with numerous other claims (including: high levels of cerebral lactates, downregulation of proteins involved in the Krebs cycle and electron transport chain, increased levels of ROS in patients with BD), allowed the formulation of the mitochondrial hypothesis, proposing a role of mitochondrial dysfunction in the genesis and progression of BD[204]. Abnormalities of these organelles, and the resulting oxidative stress, lead to activation of TLRs and inflammasome, stimulating the production of pro-inflammatory cytokines and inducing the activation of the immune system[274].

Immuno-inflammatory imbalance

The presence of immune dysfunction in BD is supported by numerous evidence showing high levels of pro-inflammatory cytokines in patients. An important consequence of the immune dysfunction and pro-inflammatory status observed in BD is the activation of the kynurenine pathway, the metabolites of which are associated with neurodegeneration, neurotoxicity and neurotransmission alterations, due to reduction of serotonin stores**[275, 278]**: the set of these processes could contribute to the structural and functional alterations observed in the brain of patients with BD**[202]**.

Chronobiological considerations

The transition from euthymia to mania has been associated with an increase in catecholamine production[279] and disturbed sleep patterns in unmedicated euthymic individuals. Total sleep deprivation can exacerbate manic symptoms in

up to 30% of bipolar patients and produce manic-like behavior in healthy controls(85). These results lend credence to the social rhythm disruption or social zeitgeber hypothesis of mood disorders, which posits that a disruption in social/biological cycles may trigger emotional outbursts in sensitive individuals[128]. Consequently, circadian rhythm abnormalities play a crucial role in the genesis of BD, and all successful therapies try to resynchronize the biological clock.

In this regard, it should be noted that seasonal variations are among the most important environmental triggers for the onset of mood disorders[5]. In fact, seasonal affective disorder (SAD) causes sensitive people to have depressed episodes throughout the fall and winter months, when the days get shorter. Early morning bright light treatment has a phase advancing impact and is beneficial in SAD, but it has also been linked to transitioning into mania and creating mixed emotions[281].

Clock genes in bipolar disorder

BD has also been connected to genes involved in the circadian mechanism. In one study, the causal relationship between SNPs in 10 CLOCK-related genes (ARNTL, CLOCK, CRY2, CK1, DBP, GSK3, NPAS2, PER1, PER2, and PER3) was studied. Haplotype analyses of the ARTNL and PER3 loci in 159 families found a significant correlation with BD[168].

Significantly, mutant mice models developed genetically have offered light on the role of circadian genes in mood disorders. A mutation introduced into the Clock gene (Clock19) creates mice with manic-like characteristics. Intriguingly, when these animals were given the prototypical mood stabilizer, lithium, their behaviors resembled those of wild type mice in substantial part[196]. Mutations in other CLOCK genes also result in comparable behavioral problems; for instance, transgenic mice overexpressing GSK3 have manic-like patterns[52]. Using Clock19

mice, researchers discovered a relationship between circadian genes, neurotransmitter functional modulation, and clinically significant behavioral characteristics.

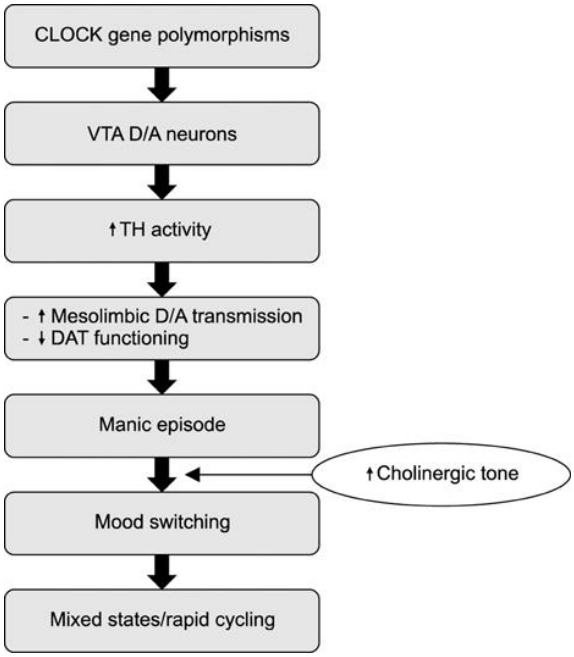

Figure 1 depicts diagrammatically the emerging evidence for the pathophysiology of mood flipping and the generation of mixed symptoms in BD.

Infections

A recent meta-analysis examined the association between BD and prenatal or perinatal infections: five of the eleven studies analyzed demonstrated an association between Cytomegalovirus (CMV) antibody levels and BD, while two studies reported an association between maternal infection with Orthomyxovirus and BD with psychosis, although other studies did not find an association[15].

More evidence supports the link between BD and T seropositivity. Gondii, with an increased likelihood of BD in those who have igG for T. Gondii[217]. To support these findings, T. Gondii infection has been discovered to induce alterations in dopamine metabolism, leading in an increase in this neurotransmitter's synthesis[282], a mechanism that may play a role in the onset of manic episodes in BD46. In addition, there is evidence that adhering to T. gondii, the metabolism of dopamine is altered, resulting in an increase in this neurotransmitter's production. Gondii,

the local inflammatory response changes the levels of BD-involved cytokines, specifically IL-6 [283].

Pharmacological triggers of switching

It is known that individuals with bipolar depression treated with different kinds of antidepressants have varying rates of transition into manic or hypomanic states, and that mixed episodes occur more frequently under these conditions. On several occasions, long-term therapy with tricyclic antidepressants (TCAs) has been associated with this affective alteration in up to 70% of recipients. TCAs inhibit serotonin and norepinephrine re-uptake from the synaptic cleft, and these combined blockers produce manic/hypomanic shifts more frequently than specific serotonin re-uptake inhibitors[129]. Bupropion, a dual norepinephrine/dopamine re-uptake inhibitor, also induces switches in approximately 20% of treated patients, despite co-treatment with mood stabilizers. Even in the presence of mood stabilizers, it appears that increasing synaptic levels of norepinephrine or dopamine by inhibiting reuptake stimulates the transition from depression to hypomania or mania as well as the development of mixed states[186].

In contrast, increasing levels of norepinephrine and dopamine causes manic-like behavior immediately. For example, the therapeutic administration of L-dopa to individuals with Parkinson's disease may result in mania-like behaviors. Indirect dopamine/norepinephrine augmentation by amphetamine, a mixed reuptake inhibitor, can also induce manic/hypomanic exacerbations in euthymic bipolar patients and mania-like behavior in healthy individuals. Changes in dopamine/norepinephrine reuptake sites can impact the behavioral effects of amphetamine, according to studies[226].

Since Tyrosine hydroxylase (TH) is the rate-limiting enzyme in dopamine synthesis, injection of the TH inhibitor -methyl-para-tyrosine (AMPT) depletes catecholamines, decreases manic symptoms, and increases depressive symptoms.

In one study, hypomania was created in euthymic bipolar patients following recovery from an AMPT-induced reduction in catecholamines, indicating that catecholamine control is necessary for transitioning to an active state, although the opposite may be true for depression[7, 62].

Less is known about medicines that may induce a depressive episode. A drug used to aid memory in Alzheimer's disease, physostigmine, is an acetylcholinestrase inhibitor that blocks the breakdown of acetylcholine, hence increasing synaptic levels, reduces manic symptoms in patients with bipolar disorder, but can cause depression in healthy persons and patients in remission. Recent research indicates that elevated levels of acetylcholine are associated with both unipolar and bipolar depression[284]. In addition, the expression of cholinergic receptors is altered in bipolar individuals, lending credence to the idea that elevated acetylcholine levels promote depression in BD patients[285].

Lamotrigine and Riluzole are both glutamate release inhibitors; however, none has been associated with the switch process. Additionally, lacking further evidence of ketamine-induced switching in persons with bipolar depression[286], glutamatergic signaling is unlikely to play a role in the switching process[287].

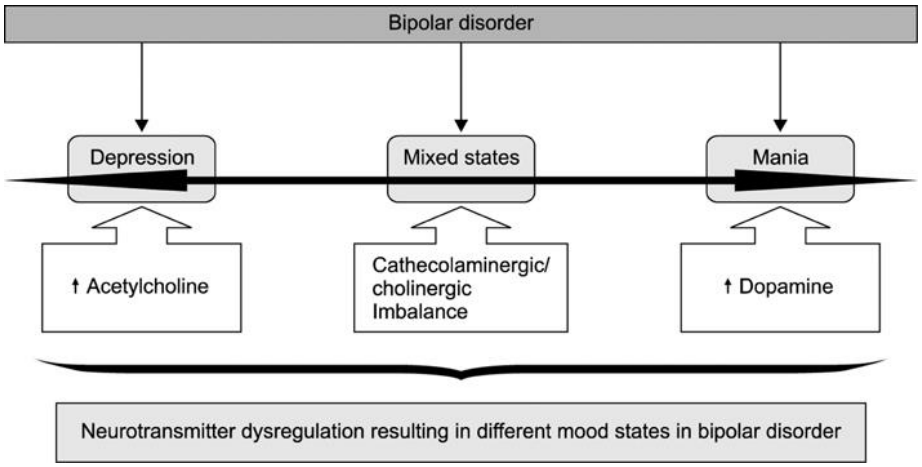

Figure 2 depicts an illustrative application of the neurochemical imbalance hypothesis of bipolar disorder, highlighting the disease-long persistence of symptoms.

Child abuse

Extensive evidence supports child abuse as a risk factor for developing bipolar disorder (BD)[29]. The most significant associations with BD concern cases of previous physical, sexual, and emotional abuse, as well as physical and emotional neglect[288]; the strongest of these is for emotional abuse, which was found four times more frequently in patients with BD than in controls[288]. In addition, BD patients have a greater incidence of early hardship.

In addition to being a risk factor, child maltreatment is associated with a worse clinical course of bipolar disorder, including more severe and frequent episodes, an earlier age of onset, an increased risk of suicide, and psychiatric comorbidity[289].

The mechanism through which childhood traumatic events increase the risk of bipolar disorder (BD) is unknown; nevertheless, these events are associated with the onset of emotional dysregulation, hostility, and impulsivity, which may explain this association[65].

Alterations at the hypothalamic-pituitary-adrenal[290] axis, increased levels of BDNF and cytokines pro-inflammatory[291] and reduced volume of gray matter at the level of the limbic [292] system observed in patients with history of childhood abuse constitute a possible neurobiological substrate through which childhood trauma can be related to BD.

Psychological stress

There is an increased risk of bipolar disorder (BD) onset in the first six months after a major stressful event; however, the rate of stressful events prior to the onset of BD has been found to be comparable to that of major depression[111]. Particularly

stressful events (in particular the suicide of a first-degree relative) have been found to be associated with an initial hospitalization for a manic episode, despite the fact that the association has many confounding factors, such as the presence of other mental disorders[111, 117].

Substance abuse

BD frequently occurs in comorbidity with substance abuse disorder (SUD)[293]. Due to the difficulty in establishing the temporal connection between SUD and the onset of BD, this is difficult to demonstrate.
Numerous studies show a correlation between cannabis use and the recurrence of manic symptoms; two prospective studies indicate that cannabis use triples the risk of occurrence of subthreshold manic symptoms, and a third study found that the risk of a first episode of bipolar disorder increased fivefold in cannabis users, demonstrating a dose-response relationship[294].

Other drugs explored for their possible role in the start of BD include opioids, which have been associated with an elevated risk of DB[205], and alcohol: researchers found that drug and alcohol misuse or addiction before the age of 25 increased the probability of developing BD[252].

Despite the results presented, numerous confounders remain in the analysis of the associations between BD and SUD: for instance, it has been suggested that cannabis use may serve as self-medication in patients with bipolar symptoms under-leaf prior to the onset of BD[295], which would explain the above results; furthermore, there is evidence that the same genetic factors increase the risk of developing both BD and SUD 65, and that child abuse is associated with both of these disorders[3].

1.4 PHYSIOPATHOLOGY **[143]**

In 2022 authors such as Magioncalda [143] published an interesting theory, which proposes a unified model of the possible pathophysiology of bipolar disorder, of which the main concepts are reported in this paragraph.

Immunological alterations

Evidence of immunological dysregulation and inflammation in BD, have been accumulating since first described by Maes [8, 14, 103, 121, 142, 190, 296] regarding cytokines and immune cells in the peripheral circulation and central nervous system. Particularly, levels or activity of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF), interferon (IFN), and other soluble factors such as C-reactive protein (CRP), were consistently elevated during the active phases of bipolar disorder (BD), mania, and depression, with complete or partial normalization during euthymia[70, 297]. In addition, activation of T cells with increased levels of circulating CD4+ T cells and decreased levels of CD8+ T cells, as well as activation and increased peripheral levels of monocytes and activation of microglia, have been frequently found in BD[33, 118, 187, 190, 222, 298–300]. This pattern was substantially related with Bipolar Disorder (BD) patients recruited during mania, but it was less obvious in individuals recruited during depression or euthymia[146].

These findings may indicate that BD is associated with an immune activation profile that is mostly pro-inflammatory.

Changes in gray and white matter of the brain

Gray matter (GM) abnormalities have been identified in BD, albeit with variable results [27, 110]. In the initial episode and early stage of BD, no changed GM volumes were detected[28, 228]. Evidence of extensive neuroprogressive loss of GM volume, particularly in the frontal regions, has been revealed in longitudinal investigations

and is associated with longer disease duration; this is connected with progressive cognitive decline in BD[301, 302].

Multiple structural imaging investigations have demonstrated that white matter (WM) abnormalities are a constant finding in BD. Importantly, extensive WM structural abnormalities were then observed in BD[28, 93, 170, 170, 227, 303]. The greater and most consistent WM changes in BD were found in the cingulum and corpus callosum, as well as in frontal areas, parahippocampal areas, and tracts such as the uncinate fasciculus and fornix, which mostly connect regions of the limbic system (138,141-144). As observed, extensive WM abnormalities were primarily visible in patients recruited during the active phases of the disease, but WM alterations localized in the front midline structures were characteristic of all phases of BD[145], with the most consistent WM changes and structural connection abnormalities in the anterior midline regions in participants recruited during manic episodes[146, 151]. Neuropathological data in BD demonstrated persistent reductions in the number or density of oligodendrocytes, as well as myelin abnormalities, particularly in anterior brain regions[203, 304, 305]. These findings are comparable with the WM alterations observed in imaging investigations.

Relationships between changes in white matter and the immune system.

The BD link between WM changes and the decrease in circulating terminal effector CD8+ T lymphocytes was observed only for terminal effector CD8+ T cells, but not for other cells such as CD4+ T cells[146]. WM changes were also observed to correlate with cytokine levels in BD, including TNF and IFN[306].

These data may indicate that BD is associated with an immune response sustained by CD4+ T cells that leads to activation of CD8+ T cells and an inflammatory state, and that activated effector CD8+ T cells may migrate into brain tissue, where their cytotoxic effects may contribute to widespread WM damage, which most frequently affects tracts connecting limbic regions.

Altered networks in the limbic

The limbic network (LN) is responsible for the stress-related modulation of homeostasis and neurotransmitter signaling [56, 172, 307, 308]. Authors[8, 14, 103, 121, 142, 190, 296] have explored and consistently identified abnormalities in the LN in depressive and bipolar illnesses. Specifically, a localized decrease in grey mass volume was observed in the subgenual anterior cingulate cortex and orbitofrontal cortex in BD[70, 297], accompanied by a decrease in glia without an equivalent decrease in neurons. Multiple studies [309] have found that BD is characterized by an enlarged amygdala and a shrunken hippocampus, as well as a structural network dysconnectivity[127, 310] across several limbic areas. Lastly, state-dependent changes in the metabolic activity of the subgenual anterior cingulate and orbitofrontal cortices, as well as increased baseline metabolism in the amygdala and hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis (especially during mania), have been strongly linked to BD[25, 154, 309]. Importantly, it appears that the structural damage in the Limbic network in BD is related to metabolic overactivity[309]. Consequently, regulation of hyperactive limbic regions was observed to alleviate clinical depressive symptoms[196].

All these findings may suggest that BD is characterized by immune-mediated WM damage and that its unique localization in the LN may play a crucial role in the disorder's pathogenesis.

Stress response, inflammation, and neurotransmitter signaling alterations

The LN may play a complex role in the interplay between stress response, inflammation, and dysregulation of neurotransmitters[296]. Stress-induced activity in the LN is related to temporary increases in dopamine (DA) and norepinephrine signaling, opioidergic signaling, and HPA axis activity, as well as alterations in

serotonin (5HT) metabolism[36, 41, 183, 184, 186]. In addition, stress response's hormones modulates immune cell activity by acutely inducing a Th2 shift in the Th1/Th2 balance and chronically causing low-grade inflammation characterized by increased pro-inflammatory factors, such as IL-6, IFN, and TNF[61, 296, 311]. Intriguingly, stress system activation is related with increased susceptibility to infections, particularly viral illnesses; for instance, latent herpesvirus can be reactivated during stress responses[296]. Infection with CMV (or also toxoplasma gondii) has been observed to be associated with depressed or bipolar illnesses [5]. Thus, in the presence of immunological dysregulation, viral reactivation may lead to inflammation and brain injury[234]. Consequently, pro-inflammatory mediators can affect neurotransmitter transmission[160, 166, 201, 296]. Pro-inflammatory cytokines, such as IFN, TNF, and IL-6, increase the activity of the indoleamine 2,3-dioxygenase (IDO) enzyme, which diverts tryptophan away from 5HT production and promotes the kynurenine pathway[160, 166, 201, 296]. This decreases the availability of 5HT and leads to the production (by activated microglia) of various metabolites, such as quinolinic acid (capable of activating NMDA receptors, potentially inducing excessive glutamate signaling and related excitotoxicity) and kynurenic acid (an NMDA receptor antagonist)[201, 296]. In consequence, alterations in frontal glutamatergic NMDA-mediated signaling may influence both DA and 5HT signaling (which are mostly decreased or enhanced by NMDA receptor agonists or antagonists, respectively)[312]. In addition, TNF and IL-1 trigger mitogen-activated protein kinases (MAPKs), which enhance the expression and function of monoamine transporters, hence decreasing the synaptic availability of neurotransmitters such as 5HT and DA[160]. Consequently, it has been demonstrated that inflammatory stimuli elicit a decrease in DA release in the basal ganglia, as well as reduced activation of the ventral striatum and emotional blunting, in both healthy and depressed persons[160]. In depressed patients, increased levels of inflammatory markers, possibly along with related DA reductions, were associated with functional disconnections between ventral striatum and ventromedial prefrontal cortex (correlating with anhedonia) and between dorsal striatum and supplementary motor area (correlating with psychomotor inhibition)[160]. It is important to note, however, that decreased 5HT

availability has been found to generate a functional disconnection of the 5HT-producing brainstem nuclei exclusively in patients with affective disorders[313].

These findings imply that stress response and inflammation are physiologically capable of inducing changes in neurotransmitter availability, which could pathologically influence the functional architecture of brain activity in BD, possibly in relation to structural abnormalities in the LN.

Brain activity alters intrinsically

Since the 2000s, functional MRI investigations of resting-state brain activity have identified abnormalities in the functional architecture of intrinsic brain activity in BD. As previously described, abnormalities in subcortical–cortical functional connectivity (FC) have been related with BD. In addition, Anticevic et al.[10] discovered in BD an increase in FC between the thalamus and sensorimotor cortical areas, as well as a decrease in FC between the thalamus and associative frontal cortices; Functional changes were also identified in the sensorimotor network, salience network, and central executive network in BD [54, 144, 314–316]. However, results are varied and contradictory at times, possibly reflecting the clinical variability of BD.

Neurotransmitter signaling changes.

As previously mentioned[149], it has been observed a functional disconnection of neurotransmitter-related nuclei in BD, with varied patterns over the various periods of the disease. Mania diminished the FC between 5HT-related raphe nuclei and basal ganglia-thalamic areas[149]. In depression, the FC between DA-related substantia nigra and basal ganglia-thalamic areas was diminished [87]. Specifically, decreased 5HT transmission in BD, and particularly in the manic phase, and

decreased DA transmission in the depressive phase have been described as the most consistent neurotransmitter findings in BD[317, 318].

Subcortical–cortical loop changes

It's been verified the thalamus-SMN hyperconnectivity in our BD demonstrated by a specific pattern of changes during the active phases of the disease[149]. In particular, the thalamus-SMN FC increased from predominantly negative connectivity in healthy participants to predominantly positive connectivity in mania, demonstrating an aberrant coupling of thalamus and SMN signals[149]. In contrast, the thalamus-SMN FC increased from predominantly negative connectivity in healthy subjects to approximately zero connectivity in depression (with inhibited psychomotricity), reflecting a decrease in the absolute strength of correlation (i.e. dissociation) between thalamus and SMN signals[149]. In addition, the thalamus-SMN FC was unaltered in euthymia, whereas it was elevated in agitated depression (akin to mania rather than inhibited depression, suggesting a particular relationship between thalamus-SMN FC and psychomotor changes)[149].

Significant network modifications

Neuronal variability was shown to be distributed differently across the brain of BD patients during the active phases of disease[150]. Specifically, the ratio between neuronal variability in the SMN and DMN (in the ultra-low frequency band slow5 [319]) was increased in, and decreased in depression, whereas no changes were observed in euthymia[150]. In addition, was detected an aberrant global signal representation in the BD, which was higher in SMN regions during mania and DMN regions during depression[233]. Moreover, we observed a reduction in intra-network FC within the DMN in mania and within the SMN in depression[317, 318] with distinct changes in regional homogeneity and degree of centrality in the BD phases: regional homogeneity and degree of centrality were decreased in the DMN during mania; on the other hand, regional homogeneity was decreased in

the SMN during depression[197]. Notably, all these alterations in intrinsic brain activity correlated in an opposite manner with manic and depressive symptomatology[144, 150, 151, 197, 233]. In addition, some authors have reported network changes during the various phases of BD. Network hyperconnectivity and increased clustering in the superior frontal gyrus, amygdala, and midbrain (including the DA-related SNC and ventral tegmental area, VTA) have been linked to manic symptoms[215]. In contrast, depression was associated with decreased amplitude of low-frequency fluctuations in SMN regions and increased amplitude in SN regions[320]. In depressive DMN areas, increased regional homogeneity was seen[136].

Mania may be associated with a functional disconnection of the 5HT-related RNi, an increase in thalamus-SMN FC toward positive values, and a relative increase in SMN activity along with a decrease in DMN activity (consistent with the observed negative correlation of RNi-related FC with thalamus-SMN FC and SMN activity in healthy subjects)[41, 149, 150]. In contrast, depression may be associated with a functional disconnection of the DA-related SNC, a decrease in thalamus-SMN FC toward around-zero values, and a relative decrease in SMN activity along with an increase in DMN activity (consistent with the observed positive correlation of SNC-related FC with the absolute value of thalamus-SMN FC and SMN activity in healthy subjects) [41, 149, 150]. Thus, these findings may suggest that the manic and depressive phases of bipolar disorder are characterized by distinct functional reconfigurations of intrinsic brain activity, including changes in neurotransmitter signaling, abnormal subcortical–cortical coupling, and alterations in network balancing.

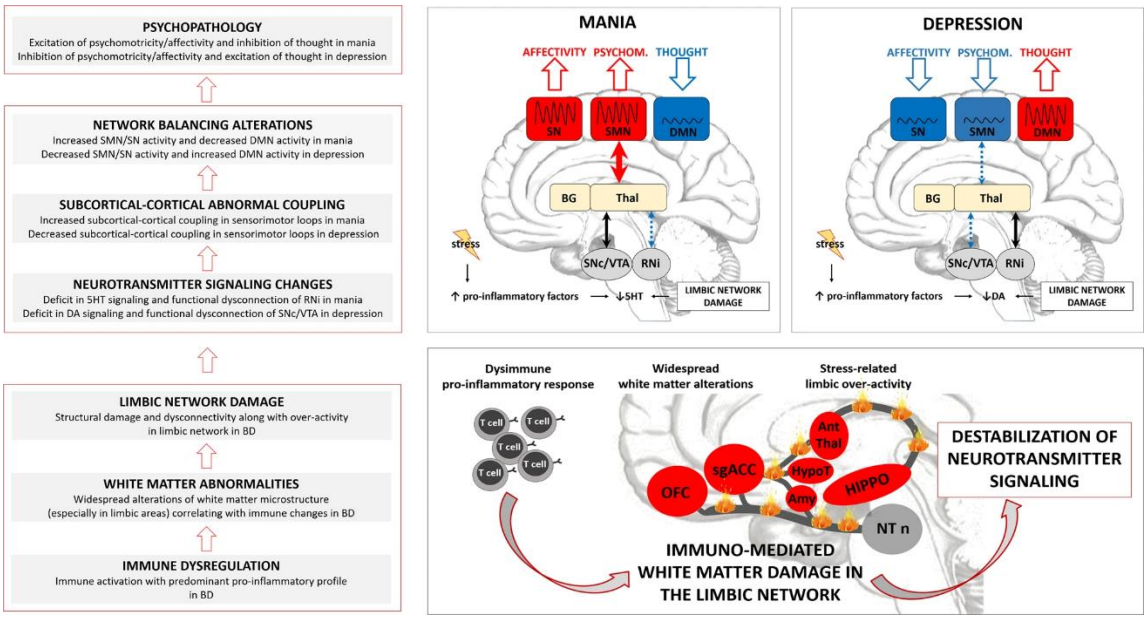

Figure 3

1.5 Clinical presentation and diagnostic criteria[182]

Subtypes [199]

There are five different varieties of bipolar disorder. All three categories are characterized by distinct shifts in mood, energy, and activity levels. These moods range from moments of excessively "up," happy, irritated, or energized behavior (known as manic episodes) to periods of severely "down," melancholy, apathy, or hopelessness (known as depressive episodes). Hypomanic episodes are less intense manic episodes.

- *Bipolar I disorder* is characterized by manic episodes lasting at least 7 days (almost every day for most of the day) or by manic symptoms so severe that the individual requires immediate medical care. Often, depressed episodes also occur, typically lasting a minimum of two weeks. Also conceivable are episodes of depression with mixed features (exhibiting both depressive and manic symptoms). Rapid cycling is defined as

experiencing four or more episodes of mania or depression within one year.

- *Bipolar II* disorder is characterized by alternating periods of depression and hypomania. In bipolar II disorder, Hypomanic episodes are less severe than manic episodes.

- *Cyclothymic disorder* (also known as cyclothymia) is characterized by recurring hypomanic and depressive symptoms that do not meet the criteria for hypomanic or depressive episodes.

Other specified and unspecified bipolar and related diseases: occasionally, a person may exhibit bipolar disorder symptoms that do not fit the three categories given above; these are known as

- *bipolar disorder and associated disorders due to an underlying medical and pharmacological condition,* the humoral alteration develops in the context of intoxication or withdrawal from psychoactive substances, or there is evidence that humoral impairment is the direct consequence of an underlying medical condition.

- *Bipolar disorder and related disorders without specification,* it does not specify why the criteria for a specific bipolar disorder and related disorders are not met.

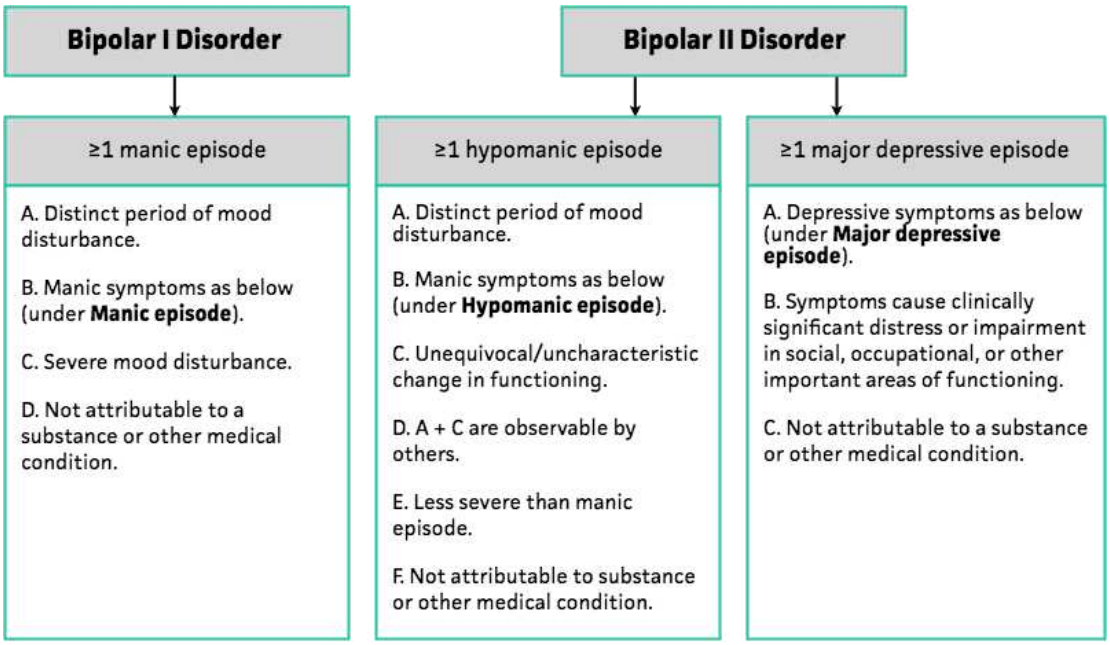

Figure 4 [321]

Manic and hypomanic episode[194]

Manic and hypomanic episodes are defined by a symptomatology that encompasses psychic, somatic, and behavioral[194] aspects; what differentiates the maniacal episode from the hypomanic event is that psychotic symptoms are missing in the hypomanic episode[182].

Affective sphere in a manic or hypomanic episode, the patient displays a noticeable exaltation of mood (hyperthymia, in the most severe cases euphoria), which is frequently followed by a rapid transition to a state of dysphoria-irritability, which can intensify until the start of angry episodes.

Cognitive sphere One can observe ideational acceleration, which can be accentuated to the point of hesitating in a flight of ideas, as well as alteration of attention (greater distraction) and pathological increase of self-esteem (hypertrophy of the ego), which can manifest in the most severe episodes as delusional ideas of greatness (genealogical delirium, power, erotomanic, mystical-religious). It is not uncommon for a manic episode to be accompanied by

hallucinations, typically of the acoustic-verbal variety (commenting voices, conversational voices, or echo of thought).

Somatic symptoms Typical of the manic episode is the patient's perception of an increase in energy, despite a reduction in the hours of sleep (there is a delay in falling asleep and an early awakening), as well as an increase in libido, appetite, and a loss of weight due to the increase in energy expenditure caused by hyperactivity.

Behavioral symptoms the patient exhibits a propensity for logorrhea (which, in the most severe forms, can evolve into a loss of the logical sense of language), hyperactivity (with initiatives that become increasingly chaotic and unproductive in the most severe forms of mania), behavioral disinhibition, impulsivity, and the execution of inappropriate and excessive expenditures. Psychomotor agitation with notably erratic behavior, or even the sudden onset of psychomotor arrest, may manifest in more severe cases (manic stupor).

Table I Diagnostic criteria for manic episode according to DSM-5

A. A defined period of abnormally and persistently elevated, expanded or irritable mood and abnormal, persistent increase in purposeful activity or energy, lasting at least one week and present for most of the day, most days (or of any duration, if hospitalization is required)

B. During the period of mood alteration and increased energy or activity, three (or more) of the following symptoms (four, if the mood is only irritable) are present at a significant level and represent a noticeable change from habitual behavior:

   1. Hypertrophic self-esteem or grandiosity
   2. Decreased need for sleep
   3. More talkativeness than usual or push keeps talking
   4. Escape of ideas or subjective experience that thoughts follow one another quickly
   5. Distractibility, reported or observed
   6. Increased targeted activity (social, work, school or sexual) or psychomotor agitation (unmotivated non-finalized activity)
   7. Excessive involvement in activities that have a high potential for harmful consequences (such as uncontrolled purchases, unseemly sexual behavior, or rash financial investments)

C. The alteration of mood is severe enough to cause a marked impairment of social or work functioning or to require hospitalization to prevent harm to oneself or others, or psychotic manifestations are present

D. The episode is not attributable to the physiological effects of a substance (substance of abuse, medication, or other treatment) or other medical condition.

Table II Diagnostic criteria for the hypomanic episode according to DSM-5

A.	A defined period of abnormally and persistently elevated, expanded or irritable mood and abnormal, persistent increase in purposeful activity or energy, lasting at least four consecutive days and present for most of the day, most days.
B.	During the period of mood alteration and increased energy or activity, three (or more) of the following symptoms (four, if the mood is only irritable) are present at a significant level and represent a noticeable change from habitual behavior:
	1. Hypertrophic self-esteem or grandiosity;
	2. Decreased need for sleep;
	3. More talkativeness than usual or push keeps talking;
	4. Escape of ideas or subjective experience that thoughts follow one another quickly;
	5. Distractibility, reported or observed;
	6. Increased targeted activity (social, work, school or sexual) or psychomotor agitation (unmotivated non-finalized activity);
	7. Excessive involvement in activities that have a high potential for harmful consequences (such as uncontrolled purchases, unseemly sexual behavior, or rash financial investments).
C.	The episode is associated with an obvious change in functioning, which is not characteristic of the individual when he is asymptomatic.
D.	Mood alteration and change in functioning are observable by others.
E.	The episode is not severe enough to cause a marked impairment of social or occupational functioning or to require hospitalization. Absent psychotic manifestations.
F.	The episode is not attributable to the physiological effects of a substance or other medical conditions.

*Depressive episode**[194]***

The depressed syndrome that occurs in bipolar disorder patients is remarkably similar to that of major depression[92], with a modest incidence of hypersomnia, hyperphagia, and psychotic symptoms[155, 165].

Emotional sphere the patient suffers from mood depression, characterized by feelings of dejection and pervasive melancholy, anhedonia, and the frequent presence of dysphoric-irritable mood, with rage and hostility that can be triggered by even minor triggers.

Cognitive sphere Typical of a major depressive episode are the ideational slowdown, difficulty with memory and concentration, and cognitive distortions, which lead to a pessimistic view of reality, a sense of insecurity and indecision, and the manifestation of guilt and self-blame, which can lead to thoughts of death and suicidal ideation.

Somatic symptoms in a major depressive episode, the patient experiences a drop in energy (asthenia and easy fatigability), along with a decrease in libido and appetite. Insomnia, which frequently appears as terminal insomnia, is another characteristic feature (early awakenings).

Behavioral symptoms Depression is characterized by alterations in psychomotor behavior (both slowness and restlessness, most usually the former), as well as a tendency to weep, disregard clothes and self-care.

Table III Diagnostic criteria for major depressive episode according to DSM-5

A.	Five (or more) of the following symptoms were simultaneously present during a two-week period and represent a change from the previous level of functioning; at least one of the symptoms is 1) depressed mood or 2) loss of interest or pleasure.
	1. Depressed mood for most of the day, most days, as reported by the individual or as observed by others;
	2. Marked or decreased interest or pleasure in all, or almost all, activities for most of the day, most days (as indicated by subjective reporting or observation
	3. Significant weight loss, not due to diet, or weight gain, or decreased or increased appetite most days;
	4. Insomnia or hypersomnia most days;
	5. Psychomotor agitation or slowing down most days (observable by others);
	6. Fatigue or lack of energy most days;
	7. Excessive or inappropriate feelings of self-devaluation or guilt (which can be delusional), most days;
	8. Reduced ability to think or concentrate, or indecision, most days (as a subjective impression or observed by others);
	9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan or suicide attempt or a specific plan to commit suicide.
B.	Symptoms cause clinically significant distress or impairment of functioning in social, work, or other important areas.
C.	The episode is not attributable to the physiological effects of a substance or other medical condition.

Mixed episode

It is configured as a state in which typical symptoms of the depressive and manic phase are present at the same time. At a purely diagnostic level, the category "mixed mood episode" has been eliminated in the DSM-5, while the DSM-IV-TR is present. Instead, the term "episode *with mixed features specifier"* has been introduced, which applies when at least three subthreshold symptoms of the opposite polarity are present during a mood episode, and which can consequently be attributable to the manic episode in DB I, the hypomanic episode in BD-I and BD-II, the major depressive episode in BD-I and II and major depressive disorder (MDD). [155]

Despite these innovations, the diagnosis and characterization of these episodes remains complex. A possible solution has been proposed by the introduction of the ACE model, which aims to describe the clinical manifestations of mood disorders no longer by subjecting them to the macro-categories of “mania” or “depression”, but by observing them as alterations of three distinct functional domains: *Activity, Cognition* and *Emotion*.[322]

According to this model, therefore, the episodes with mixed characteristics would be manifestation of fluctuations “asynchronous” between them of these three domains, with different characteristics from episode to episode, based on the domain more altered.

1.6 Diagnosis

The diagnosis of bipolar disorder is performed based on a comprehensive clinical assessment, and is supported, whenever possible, by the collection of information obtained from third parties, which may be the family members of the patient.
Unfortunately, no biomarkers are available to date that can inform about diagnosis, severity and prognosis of bipolar disorder, making a longitudinal clinical evaluation of the patient necessary[155]. The diagnostic criteria for BD-I, BD-II and Cyclothymia are presented in Figure 4.
There are also numerous scales of evaluation (both self-administered and hetero-administered) that can help the clinician in the recognition of clinical characteristics suggestive of a diagnosis of bipolar disorder: among the most important are the Bipolar Inventory Symptoms Scale[31], the Screening Assessment of Depression Polarity[212], the Hypomania Checklist[9] e la Probabilistic Approach for Bipolar Depression.[323]

DIFFICULTIES AND CLINICAL STRATEGIES IN THE DIFFERENTIAL DIAGNOSIS OF BIPOLAR DISORDER

Why is bipolar disorder so difficult to diagnose accurately?

BD is a difficult disease to diagnose, particularly in its early stages: only 20% of patients with BD who present with an episode of depression are correctly diagnosed in the first five years from the time they seek clinical help[324], with an average diagnostic delay of 5 to 10 years for patients with BD[325]. The differential diagnosis between bipolar disorder (BD) and major depression (DCS) remains one of the most common pitfalls faced by clinicians in these cases. Attention deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD), substance abuse disorder (SUD), and schizophrenia[155] are additional pathologies that enter differential diagnosis with BD. The high frequency of psychiatric comorbidities present in the bipolar patient adds complexity to an already difficult diagnostic challenge: the most common are anxiety disorders, which are estimated to affect up to 71 percent of cases, SUD (56%), personality disorders (36%), ADHD (20%), and eating disorders (DCA)[326]. The difficulty inherent in making a differential diagnosis and the high frequency of psychiatric comorbidities have raised the hypothesis that this is due to an inadequacy of the current diagnostic systems in describing the different pathologies: due to the current lack of understanding of the endophenotype of psychiatric diseases[327], it is forced to focus on the phenomenological manifestations of the disorder in question[177], which results in an insufficient understanding of the disorder in question[328, 329]

BD and depressive disorder

The difficulty of distinguishing bipolar disorder type I or II from unipolar depression, a condition characterized by recurrent depressive episodes, is a significant factor in the difficulty of diagnosis, particularly in patients who present during a depressive episode and who have no clear history of mania or hypomania. Unipolar depression is the most common mistake in patients with bipolar disorder type II, as they never have an episode of mania. Additionally, the incidence of depressive symptoms is greater than that of hypomanic or manic symptoms throughout the course of bipolar I or II, and these diseases frequently begin with a depressive episode. Patients with bipolar disorder type II seek treatment for depressive symptoms significantly more frequently than for hypomanic or manic symptoms, and frequently fail to recognize the consequences of the latter symptoms and thus fail to seek help for them, making identification and treatment of these symptoms particularly challenging for clinicians. Mixed mood episodes, which are characterized by both depression and hypomanic or manic symptoms, are becoming more prevalent in patients with bipolar illness.

This concept contradicts the conventional understanding of bipolar disorder as a collection of disorders characterized by discrete depressed, hypomanic, or manic episodes.

Evidence suggests that subthreshold symptoms of bipolar disorder (depressive-like, hypomanic-like, or manic-like symptoms that do not meet diagnostic thresholds for depressive, hypomanic, manic, or mixed episodes) in patients with bipolar disorder are associated with a shorter time to future relapse into full-blown illness episodes than in patients without such symptoms. Additionally, many individuals identified with unipolar depression may have undiagnosed bipolar disorder; As a result, antidepressant treatment trials for patients with unipolar depression indicate that up to two-thirds of these patients do not respond to first-line antidepressants, a third do not achieve full remission from symptoms after four treatments, and the rate of depression recurrence is very high, even in those who achieve remission after antidepressant treatment[330, 331].

Misdiagnosis of bipolar disorder type I or II as unipolar depression has many potentially negative outcomes, such as prescribing inappropriate medications and poor clinical and functional outcome. Therefore, an accurate diagnosis of bipolar illness in its early stages may assist to prevent the long-term negative effects of misdiagnosis.

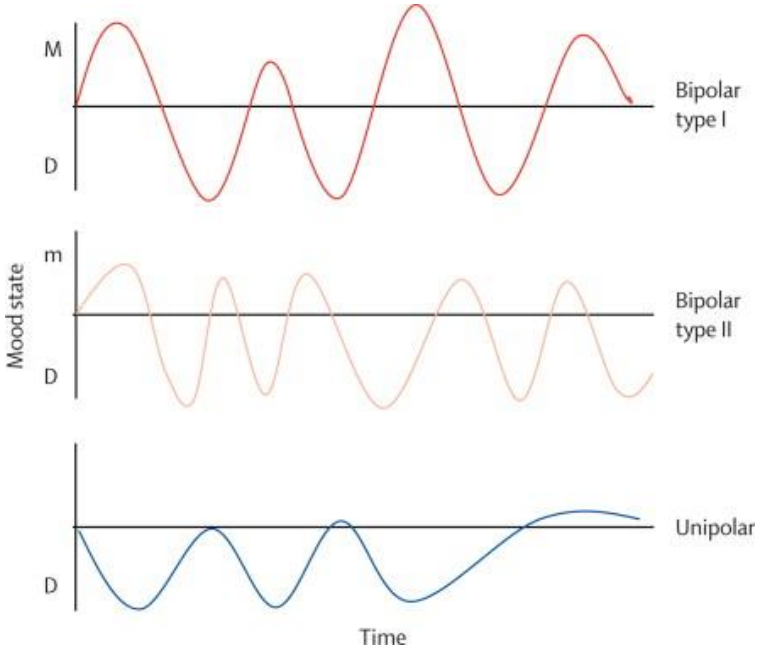

Figure 5 Mood changes over time in bipolar disorder type I, bipolar disorder type II, and recurrent unipolar depressive disorder
M=mania. m=hypomania. D=depression.

Clinical strategies to improve diagnosis of bipolar disorder in depressed patients

Several modifications have been suggested for the DSM-5 section on bipolar disorder. First, bipolar disorder and associated conditions get their own chapter. Second, the diagnostic criteria for bipolar disorder now incorporate both mood and activity or energy abnormalities. Previously, for a patient to be diagnosed with a mixed mood episode, he or she was required to satisfy the entire criteria for both mania and serious depression. A new specifier with mixed characteristics has replaced the previous criteria, therefore recognizing the presence of up to three manic symptoms within a severe depressive episode. Other revisions recognizing hypomania of brief duration will now be included in section III of the DSM-5 as a mental health illness requiring more research. Recent DSM-5 field trials reveal strong test–retest reliability of adult type I bipolar disorder[332], suggesting that DSM-5 might be a step in the right direction towards a more accurate diagnosis of bipolar disease. In addition, DSM-5 emphasizes that new dimensional measures

should be utilized in research settings to quantify psychopathology and better describe the continuum of both manic and depressive bipolar characteristics.

New self-administered and clinician-administered rating measures have been created to enhance the early identification of clinical symptoms indicative of a bipolar disorder diagnosis in individuals with a history of depressive episodes who would otherwise be diagnosed with unipolar depression. Included in these clinical characteristics are subthreshold hypomania, recurrent mood episodes, and a positive family history of bipolar illness. The Bipolar Inventory Symptoms Scale[31], the Screening Assessment of Depression Polarity[212], the Hypomania Checklist[333]. In conclusion, rigorous examination for past mania or hypomania in all depressed patients, in conjunction with supplementary information from caregivers, can aid in improving the diagnosis accuracy of bipolar illness.

1.7 Treatment

The therapeutic objectives in BD are: prevention and treatment of manic, hypomanic and depressive episodes; reduction of inter-episodic depressive symptoms; normalization of changes in the circadian rhythm; improvement and preservation of cognitive functions; treatment and prevention of medical and psychiatric comorbidities; improvement of the general quality of life of the patient; reduction of suicide[70].

Treatment of BD involves a pharmacological, psychosocial approach, and a change in lifestyle, with the main role played by pharmacotherapy.

A rapid diagnosis and a timely start to effective treatment are essential: recovery rates are in fact better in patients with a reduced number of episodes and a short duration of disease.

Despite the increasing expansion of knowledge regarding the neurobiology of BD, treatment options remain limited at present due to the absence of reliable animal models of disease on which preclinical tests can be performed.[77]

Acute phase

Manic episode

Manic episodes constitute a medical emergency that requires urgent treatment, to prevent the patient from harming himself or others. Drugs that have demonstrated antimanic efficacy are part of the class of mood stabilizers (lithium, valproate, and carbamazepine) and antipsychotics (first and second generation) (3). The recommended levels for monotherapy treatment of manic episode proposed by the International College of Neuro-Psychopharmacology (CINP)[212] are given in Table V.

LITHIUM. It is a drug with well documented antimanic properties [334], which can also mitigate the risk of the onset of post-manic depression[335]. Unique feature of lithium is its documented anti-suicidal effect, although not in acute[161]. Since it has a certain latency of effect, its use in monotherapy in acute treatment of the manic episode is limited to mild or moderate mania, provided that the patient is carefully monitored; in the case of manic episodes with psychotic symptoms, dangerous behaviors, non-compliance with treatment, its use is recommended only in association with antipsychotics, preferably second-generation. Lithium is also conventionally thought to be more effective in episodes of mania with euphoric humor[335]. The starting dose is generally 300-600 mg/day, and then arrive at a therapeutic dosage of 600-1500 mg/day: serum lithium levels during a manic episode should be between 0.8 and 1.2 meq/L. Among the disadvantages of lithium, in addition to the already mentioned reduced therapeutic range, there

is a risk of nephrotoxicity, polyuria, weight gain, hypothyroidism, tremors and teratogenicity. Prior to the start of therapy, blood count, ECG, thyroid hormone dosage and liver and kidney function evaluation are recommended[104].

VALPROATE. Used in monotherapy, has an efficacy in the treatment of acute mania superimposed on that of lithium[30], and has been shown to be more effective in the treatment of patients with BD and coexistent SUD/AUD, or with BD and episodes with mixed characteristics, Rapid cycles or mania with irritable mood[104]. When used in combination with antipsychotics, valproate guarantees a lower dosage of antipsychotics, a faster response to treatment and better results at the end of treatment[336]. Valproate can also be used in combination with lithium in patients who are not responsive.

The therapeutic range of valproate is 50-120 mcg/ml, obtained with an average dosage of 1000-2500 mcg/day; among the advantages of this drug compared to lithium there is the fastest anti-manic action[335]. Valproate may cause hepatotoxicity and an increase in ammonium levels, with the potential for encephalopathy, as well as increasing the risk of pancreatitis, thus requiring monitoring of pancreatic enzymes during treatment. Hirsutism, polycystic ovary syndrome, weight gain, tremors, alopecia and teratogenicity are documented in women of childbearing age[335].

CARBAMAZEPINE. It has proven efficacy in the acute treatment of manic episodes, both in monotherapy and in combination with other active ingredients, but is not included in the first-line treatments of numerous guidelines due to its severe side effects[336].The recommended serum carbamazepine levels are between 4 and 12 mcg/ml, with a daily dose of 400-1200 mg/day[335]. Among the advantages of this active ingredient are the lower impact on body weight, the possibility of being used in patients with concomitant neurological pathologies and the greater effectiveness in comorbidity BD-SUD[335]. Side effects of carbamazepine include hepatotoxicity, medullary aplasia, hyponatremia, teratogenicity, and Stevens-Johnson syndrome[335].

ANTIPSYCHOTIC. Among first generation antipsychotics, haloperidol and chlorpromazine have been shown to be effective in the acute treatment of

mania[337]: they have a very rapid action but cause drowsiness and extrapyramidal side effects, which is why they are reserved for the initial stages of treatment, especially in patients with agitation and exuberant behavior[335]. Second-generation antipsychotics (including olanzapine, risperidone, quetiapine) have a lower risk of extrapyramidal effects and are approved for the treatment of acute mania and also in maintenance, both in monotherapy and in association with mood stabilizers[104]. In the treatment of manic episodes, antipsychotics are administered initially at the lowest possible dose, which will then be gradually increased on the basis of effectiveness and side effects: Initial doses are 5-10 mg/day for olanzapine, 300-600 mg/day for quetiapine and 2-4 mg/day for risperidone[335]. Among second-generation antipsychotics, clozapine has been shown to be effective in patients with resistant BD, episodes with mixed characteristics or rapid cycles[338].

OTHER TREATMENT OPTIONS. Electroconvulsive therapy is an option that can be used in episodes with delirium and confusion but, since it is an invasive procedure and has negative effects on memory[339], its use is limited to cases where there are contraindications to pharmacotherapy (pregnancy, old age), resistance to therapy or catatonic symptoms[179]. Other active ingredients that have shown superior efficacy to placebo in the treatment of manic episodes are tamoxifen, allopurinol and the addition of melatonin to the treatment with lithium and risperidone[335].

Table V Recommendation levels in monotherapy treatment of acute mania. From Fountoulakis et al[75]

Treatment	**Recommendation level**	**Treatment**	**Recommendation level**
Aripiprazole	1	Lithium	2
Asenapine	1	Tamoxifen	4
Cariprazine	1	Olanzapine	2
Paliperidone	1	Haloperidol	2
Quetiapine	1	ECT	3
Risperidone	1	Pimozide	4
Valproate	1	Ziprasidone	4
Carbamazepine	2	Oxcarbazepina	4

Depressive episode

Despite the temporal predominance of depressive episodes in the course of BD, studies that have dealt with the treatment of depression in the context of this disorder are few. Currently, only four drugs are approved by the FDA for the acute treatment of bipolar depression: cariprazine, lurasidone, quetiapine and the olanzapine-fluoxetine combination. Given the limited number of approved active ingredients, it is common in clinical practice to use other drugs, often in combination, for the off-label treatment of depression in BD[36].The recommendation levels for monotherapy treatment of the depressive episode proposed by the International College of Neuro-Psychopharmacology (CINP) are given in *Table VI.*

CARIPRAZINA. It is a partial dopaminergic receptor agonist and a partial serotonergic receptor antagonist that has shown efficacy in the acute treatment of bipolar depression alone, improving in particular anhedonia and cognitive dysfunction of treated patients[340].Due to its minimal tendency to cause weight gain, and since it does not adversely affect the metabolic profile of the patient, it is considered a safe and well-tolerated drug. [155]

LURASIDONE. Similar to cariprazine, this drug has been shown to be effective in the treatment of bipolar depression, with minimal impact on body weight and no alterations in metabolic homeostasis[208].

QUETIAPINE. It is the drug with the most evidence of efficacy in the treatment of depression in both BD-I and BD-II and has also been shown to prevent the recurrence of mania and depression. However, it has significant side effects, such as sedation and drowsiness, extrapyramidal effects, weight gain and metabolic alterations. [208]

OLANZAPINE + FLUOXETINE. This is the first treatment to be approved for acute bipolar depression. In the face of a proven effectiveness, it has non-negligible side effects, causing weight gain and metabolic alterations[341].

OTHER TREATMENT OPTIONS. The use of antidepressants in the treatment of bipolar depression is controversial: despite their widespread use, there is a lack of adequate evidence to ensure their efficacy(201); the International Society for

Bipolar Disorders recommends the use of antidepressants in synergy with mood stabilizers in the treatment of patients with stable and episodic bipolar depression and in the absence of rapid cycles and history of previous destabilization associated with the use of Antidepressants[175]. There is also limited evidence that selective serotonin reuptake inhibitors (including fluoxetine and sertraline), serotonin and norepinephrine reuptake inhibitors (such as venlafaxine) and norepinephrine and dopamine reuptake inhibitors (as bupropion) can be used as monotherapy for the acute treatment of depression in BD-II patients. [155]

Other therapies that have shown superior efficacy to placebo in the acute treatment of bipolar depression are lamotrigine, ketamine, and electroconvulsive therapy. [155]

Table VI Recommendation levels in monotherapy treatment of acute depression. From Fountoulakis et al. [75]

Treatment	Recommendation level	Treatment	Recommendation level
Quetiapine	1	Olanzapine	2
Lurasidone	1	Aripiprazole	3
OFC	2	Carbamazepine	3
Fluoxetine	2	Valproate	3

Maintenance

The chronic and recurrent nature of BD makes maintenance therapy a vital tool for improving the living conditions of these patients. The objectives of maintenance therapy are the prevention of relapses, the resolution of inter-episodic symptoms, the reduction of suicidal risk and the improvement of the general quality of life of patient(188)s, pursued through an integration between pharmacological and psychosocial therapy with lifestyle interventions. [36]

Drug therapy

The recommendation levels for maintenance monotherapy treatment proposed by the International College of Neuro-Psychopharmacology (CINP)[75] are given in *Table VII.*

LITHIUM. Among the drugs, it still remains the one with the greatest evidence of efficacy in the long-term treatment of BD, guaranteeing a reduction in the risk of

manic and depressive relapse of 38 and 28% respectively compared to placebo[342]; another characteristic of the use of lithium is its anti-suicidal efficacy, documented in more than 50% of cases[343]. Despite its efficacy, the non-negligible side effects require close monitoring of the patient on therapy[77].

OTHER TREATMENT OPTIONS. There is evidence of efficacy in reducing the recurrence of mania but not of depression with regard to risperidone and aripiprazole, while lamotrigine has demonstrated long-term antidepressant effect, but not antimanic[155]. Quetiapine and olanzapine have been shown to reduce the occurrence of both manic and depressive episodes, with olanzapine also effective in preventing episodes with mixed characteristics[339].

Table VII Recommendation levels in maintenance treatment in monotherapy. From Fountoulakis et al[75]

Treatment	Recommendation level	Treatment	Recommendation level
Aripiprazole	1	Lamotrigine	2
Lithium	1	OFC	2
Olanzapine	1	Valproate	3
Paliperidone	1	Carbamazepine	3
Quetiapine	1	Venlafaxine	4
Risperidone	1	Haloperidol	4

1. Psychotherapy

Optimal management of BD requires a targeted integration between pharmacotherapy and psychotherapy[344]. Psychological approaches are based on the assumption that psychosocial stresses, such as family quarrels and other negative events that alter the sleep-wake rhythm or the achievement of personal goals, are associated with disease recurrence and worsening of symptoms in patients with BD[32].The main objectives of psychotherapy in BD are the education of patients and, where possible, *caregivers*, about strategies for managing stress and identifying early signs of relapse, as well as education in a regular lifestyle and healthy habits[159]. Moreover, given the high rates of non-adherence to pharmacological treatment in patients with BD[345], psychosocial treatment also ensures continuity of pharmacological treatment[32].

Among the types of psychotherapy that have shown some efficacy in the long-term treatment of BD (again in combination with drug therapy) are family therapy, *cognitive and functional remediation* therapy, interpersonal and social rhythm therapy, and psychoeducation [224].

Lifestyle

Education to a correct lifestyle and monitoring of the physical health of patients with BD are fundamental, due to the high rates of medical comorbidities, sedentary lifestyle, incorrect food choices, cigarette smoking [346] habit (it is estimated that about 40-60% of patients with BD smoke tobacco) that characterize these patients. [155]

2. EMOTIONS AND RELATED PROCESSES

Emotions impact how we think, feel, and behave, yet it is not simple to describe what an emotion is, since there are many numerous ways to conceive it[87]. However, despite considerable variances, three major points of agreement are clear throughout the various methods[86].

First, emotions entail changes in the neurocognitive experience, behavior, and peripheral physiology[153]. Indeed, emotions entail not only changes in the subjective experience, but also influence the condition of the environment, through the actions of the individual[347]. Some of the components of behavior that emotions affect are expression, posture, and situation-specific instrumental actions such as retreating or striking [83]. Emotions also entail neuroendocrine and autonomic adaptations that predict and/or accompany emotion-related activities[119].

Moreover, emotions emerge throughout time, in seconds to minutes.[44] One approach of characterizing these emotion dynamics is to utilize the "situation-attention-appraisal-response sequence"[16]. This process starts with a psychologically significant circumstance, that might be referenced to internal representations or to elements of the external world [83]. These scenarios are then judged in a "good for me- terrible for me" assessment, by reflecting the individual's currently active aims[153]. It is this contextually based appraisal that activates a multi-componential series of events (physiological, cognitive, behavioral, and subjective acts) that constitute emotion [83].

Lastly, emotions may be either useful or destructive, depending on the circumstance. Emotions may be useful when they facilitate decision making , give information on the optimal course of action, tell us about others' behavioral intentions, and inspire socially accepted behaviors [86]. In contrast, emotions may be detrimental when they are the inappropriate frequency, strength, length, or kind for a given context, and drive maladaptive actions[88].

In opposition, emotions may be detrimental when they are the inappropriate incidence, strength, length, or kind for a given context, and drive maladaptive actions [86].

In conclusion, it is crucial to identify emotions from stress reactions and from mood [83]. Even though both emotions and stress responses engage whole-body reactions to relevant situations, reflexes generally refer to negative affective states caused by an incapability to solve situational demands, whilst emotions concern to more specific negative and positive affective states [124]. Unlike emotions, moods are more widespread and endure longer[78]. If mood can be considered the "pervasive and continuous 'emotional climate,'" then emotions are "fluctuating shifts in emotional weather."

2.1 EMOTION REGULATION AND RELATED PROCESSES

Emotional strategies [13]

Emotion regulation (ER) mainly refers to the skill of monitoring, analyzing, and regulating the trajectory of an emotion. ER is defined by cognitive and behavioral processes, that alters the magnitude, the content, and the persistence of the emotion [83].

These regulation tactics may be carried either deliberately or unconsciously[90]. In the first technique, also called explicit regulation, it is necessary display a deliberate effort and some level of awareness and insight. The non-conscious or implicit regulation is activated spontaneously and might be applied without the awareness of the perpetuator[347].

The emotion regulation techniques can be additionally classified in more adaptive or maladaptive, depending on its ability to ensure social adaptability and well-being to the individual [83]. Effective ER techniques relate to more beneficial short-term and long-term results in such as lower physiological arousal, greater pain tolerance, higher relationship quality, academic accomplishment, and work performance [47].

Some of these adaptative tactics are the accompanying: cognitive reframing, acceptance, active coping.

Adaptive strategies

- *acceptance*: present-moment awareness and nonjudgmental acceptance of feelings and emotional states.
- *positive reappraisal*: attributing a positive meaning to the event for personal development.
- *putting into perspective*: minimize the seriousness negative event comparing to other.
- *refocus on planning*: taking and managing the negative event.
- *Positive refocusing* thinking about happy and enjoyable problems instead of thinking about the negative event.

On the other hand the presence of patterns of emotional experience or emotional expression that interfere with goal-directed activity, due to rigid or mostly maladaptive ER strategies [47], leads to emotion dysregulation (ED). These maladaptive strategies are dramatization, negative or positive rumination, negative focus, suppression, self and other's blame, expressive suppression and avoidance[83].

Maladaptive strategies

- *Dramatization*: exaggeration in the interpretation of the negative situations.
- *self-blame*: blaming yourself for what you have experienced.
- *rumination*: recurrent pondering of the origins and effects of emotional experiences and precludes active problem solving to modify conditions around these symptoms.
- *Blaming others*: thoughts of putting the blame of what you have experienced on others.
- *expressive suppression* (example: "I keep my feelings to myself"), described as a response-focused kind of emotion management including the inhibition of emotion-expressive behavior.
- *avoidance*: is an umbrella phrase referring to an unwillingness to encounter unwanted feelings.[48]

The success of the ER is decided by the competent selection of the ER strategies and the successful implementation of the selected strategies to attain the objective[88].

Emotion regulation mechanisms

Modal model of emotion regulation claims that there are five unique emotion regulation mechanisms that occur at five moments in time[84]. These emotion control methods are classified into two groups:

First group: antecedent focused methods

- *including scenario selection*: adopting steps that make it more (or less) probable that one will be in a situation that one thinks will give birth to desired (or unwanted) feelings.
- *situation alteration:* taking measures that directly affect a situation in order to influence its emotional impact.
- *attentional deployment:* directing one's attention with the objective of affecting one's emotional reaction.

- *cognitive transformation:* adjusting one's perception of a circumstance in order to affect its emotional impact.

Second group: response focused strategies

- *response modulation:* directly modifying sensory, behavioral, or biological components of the emotional response once the emotion is well formed. [86].

2.2 THE NEURAL BASES OF EMOTION REGULATION

Multiple anatomical sites are related with emotion. At the neurological level, emotions involve highly evolutionarily conserved subcortical systems, such as amygdala, ventral striatum and periaqueductal grey (PAG), as well as a sequence of cortical areas that include the anterior insula and dorsal anterior cingulate cortex (dACC)[347].

Moreover, each structure processes information to differing levels of abstraction or inclusion of contextual information. For example, key limbic areas, such as the amygdala, ventral striatum and PAG, may extract simple motivational elements of a stimuli (for example, a snake being a possible threat). [66]

Amygdala is a key unit in the evaluation of inputs with emotional meaning. Above all, fear is the most studied emotion related to this structure. In fact, amygdala has a primary role in the subconscious estimation of the situation that generate fear, as attested by its activation in response to the presentation of a picture of a frightened face, which outcome in an immediate automatic, unconscious response, accompanied by cortical participation in a more complex response influenced by social and personal factors[12].The amygdala is also implicated in the reaction to pleasant emotions, through the link between inputs and rewards.[236] Hippocampus is crucial in controlling the impact of emotional

events, in the reaction to stressful stimuli (through linkages with the hypothalamus-pituitary-adrenal pathway), in generating negative affective states, like anxiety and stress[69]. The hippocampus may indeed give temporal and geographical context relevant to memory [347]. Additionally, cortical areas, such as the insula, may supply extra interoceptive information; and the dACC may tie the input toward other motivational demands on the individual[89].

The many connections of these areas with cortical and subcortical regions allows to integrate information both on the internal condition of the organism (e.g. heart rate, pressure, gastrointestinal motility), and on the external state, creating the foundations for appropriate functioning of the executive system[348, 349].

2.3 EMOTIONS DYS-REGULATION

ED is a multidimensional and transdiagnostic concept that regards difficulties in controlling impulsive behaviors or regulating emotional responses to negative emotions, sudden or excessively slow changes in emotions, and increased levels of affective instability, with a slower return to an emotional baseline.

It is by definition the absence of a healthy emotional regulation, which is the ability of an individual to monitor, evaluate or adjust emotional reactions, specifically in their intensity or temporality characteristics, to accomplish a goal[51].

On a further note, emotional dysregulation defines random, disorganized, and fast-cycling shifts such as multiple changes in affect, worsening in the degree of affect, abnormal acceleration of emotional fluctuation, delay in regaining the normal emotional state, and reactivity to psychosocial stimuli. [11] It could also be considered as an inability in multiples aspects of emotional regulation such as comprehension and consciousness of emotions, accepting them, controlling impulsive tendencies, behaving by following intended outcomes when

experiencing negative emotions, and utilizing efficient emotion regulation strategies and adaptability to meet targets and demands. [11]

Psychopathology

There are correlations between child emotional dysregulation and later psychopathology [11].

The processes underlying how early emotional dysregulation and later psychopathology are associated are not yet known.

Risk factors

ED often starts during early infancy. It is vital to examine parental mood disorders as hereditary and environmental variables. Children of parents with signs of depression are less prone to develop techniques for controlling their feelings and are at risk of acquiring a mood illness.[22] When parents have problems with managing their emotions, they are frequently unable to teach their children to regulate correctly. [24] The influence of parents in a child's development is recognized by attachment theory, which believes that the features of the caregiver-child interaction effect future relationships. Current research shows that parent-child interactions defined by less affection and increased animosity may outcome in children developing emotional control issues. [25] [26] If the child's emotional needs are neglected or rejected, they may face more trouble coping with emotions in the future. [27] Moreover, disagreement between parents is associated to higher emotional reactivity or dysregulation in children. [28] [29] Additionally, loss or grieving might contribute to emotional dysregulation. [30]

Overall, a history of childhood abuse, adverse experiences throughout childhood may be directly connected to emotional dysregulation, generating dysfunctional behaviors and a significant influence on functional impairment. Hence, emotional dysregulation seems to moderate the influence of childhood trauma in the global

functionality of the patient.

Clinical manifestations

Common indications of emotion dysregulation include severe tearfulness, angry crisis, or behavioral eruptions such as smashing or throwing objects, violence towards self or others, and threats of suicide. Emotion dysregulation can result in behavioral difficulties and may interfere with a person's relationships. [10]

Smoking, self-harm, eating disorders, and addiction have all related to emotional dysregulation [16]. Somatoform disorders may be characterized by a diminished capacity to manage and feel emotions or an incapacity to manifest emotions in a healthy way. [17] Individuals who have difficulties regulating emotions are at risk for eating disorders and drug misuse since they utilize food or substances to regulate their feelings. [18] [19] Emotional dysregulation is also present in those who have an elevated risk of having a mental condition, particularly an affective disease such as depression or bipolar disorder. [20] [21] Similarly, emotional dysregulation has been discovered to be widely associated with developmental disorders, such as Attention Deficit-Hyperactivity Disorder, Autism Spectrum Disorder, Obsessive-Compulsive Disorder, etc.

ED in Adolescence

In teenagers, emotional dysregulation is a risk factor for numerous mental health issues such anxiety disorders, borderline personality disorder, substance use disorder and eating disorders. Dysregulation is indeed connected with self-injury, suicidal thoughts, suicide attempts, and hazardous sexual behavior. [33] [30]

Furthermore, it has been discovered that more female youths deal with emotional dysregulation than boys [35].

ED in Adulthood

Emotional dysregulation tends to emerge as emotional responses which could appear excessive relative to the context. Individuals with emotional dysregulation may have difficulties calming down, avoid uncomfortable feelings, or focus on the negative aspects. [33] Overall, women tend to score higher on assessments of emotional reactivity than males. [36] [37] [38] A research at University College in Ireland discovered that dysregulation linked to negative feelings about individual's capacity to cope with emotions and rumination in adults. Researchers also discovered dysregulation to be widespread in a sample of persons not afflicted by mental illnesses. [39]

Impact on relationships

Emotional dysregulation plays a function in relationship's quality and pleasure. It might be challenging for emotionally dysregulated persons to establish good relationships.[24] This frequently expresses itself as severe anxiety surrounding relationships, poor capacity to create and manage boundaries, frequent and harmful disputes. [41] These sentiments may be followed by support-seeking actions such as clinging, smothering, or striving to control. [27]

The literature suggests that dysregulation enhances instances of perceived criticism, adds to physical and psychological aggression, and improves depression, anxiety, and sexual issues.[45][46][47]

Substance use

Numerous variables have been studied to explain the relationship between emotional dysregulation and drug use in young people, such as childhood abuse, cortisol levels, familial environment, and symptoms of despair and anxiety [350] investigated the correlation between childhood abuse and emotional dysregulation. Greater childhood abuse was shown to relate to an increase in difficulties controlling emotion, which in turn was associated with a higher risk of coping by using marijuana. It is been reported than higher unfavorable family emotional environment was shown to be correlated with high levels of emotional

dysregulation, which was then associated with increased drug use[115], while Prosek et all[351], explored the association between mental health and emotional control among college illicit drug users. Illicit drug users reported greater degrees of sadness and anxiety symptoms. Emotional dysregulation was more apparent among illicit substance users, in fact they manifested less insight and were less conscious of their feelings when the emotions were occurring.

Protective factors

Early encounters with caregivers can lead to disparities in emotional control. The response of a caregiver to a baby's cues can assist a newborn control their emotional systems. Caregiver engagement patterns that overwhelm a kid or that are unexpected may hinder emotional control development. Effective solutions entail working with a youngster to promote growing self-control such as modeling a desired behavior rather than demanding it. [56]

The richness of an environment, able to give adequate amounts of freedom and restraint without overstimulation or undue irritation, that a kid is exposed to supports the development of emotional control, giving the opportunities for a youngster to exercise self-regulation and practice social skills. [56]

Diagnosis

To this day, a univocal and collective definition of ED has not yet been given [47] and an inclusive view on this matter is challenging [195]. Various approaches were advanced providing a focus on specific aspects of ED.

Many tests are applied in the process of diagnosis, the most quoted are the Difficulties in Emotion Regulation Scale (DERS), the cognitive Emotion Regulation Questionnaire (CERQ), the Emotion regulation questionnaire (ERQ), the Barratt Impulsiveness Scale (BIS-11) and the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0).

These tools will be discussed in more detail in Chapter 3 “Material and methods”.

Development of more sensitive diagnostic tests to detect emotional dysregulation in bipolar disorder

This study aimed to assess the practicability and legitimacy of emotional regulation in social situations presented in 360-degree fully immersive VR environment by comparing fully/partially euthymic patients with BD, their unaffected first-degree relatives (FDRs), and healthy controls (HCs).

The present study is the first to inspect whether fully or partially remitted BD patients display irregularities in emotional regulation relative to FDRs and HCs operating an innovative virtual reality (VR) based social scenarios test (the VERA test). BD subjects manifested difficulties with down regulating their negative emotions within the novel VR paradigm in comparison to HC, that they showed no emotion regulation difference on a more traditional emotion regulation task (social scenarios task). Moreover, results presented no stepwise pattern in emotional regulatory abilities between BD, FDRs, and HCs, as predicted based on the endophenotypic criteria. Emotion regulation difficulties in BD patients were unconnected to residual symptoms, pharmacotherapy, or illness chronicity.

The findings attested suggestively reduced ability to down-regulate negative emotions in BD patients in comparison with HC in the VR paradigm, but not during standard test for emotion regulation, advising that VR may constitute a more sensitive tool relative to previous behavioral paradigms. In fact, traditional behavioral tests were incapable to detect emotional regulatory differences among remitted BD patients and controls [110].

With this premise, analysis adopting more sensitive measures during emotion regulation, such as eye-tracking and facial emotion examination, confirm abnormal emotional regulation in BD compared to HC. The evidence of impaired ability to inhibit negative emotion in patients with BD during VR is persistent with neuroimaging results of unusual neural activity during down-regulation of negative emotions in euthymic patients with BD compared to HC[122]. This suggests

the need to improved sensitivity and, possibly, increase ecological validity of the VERA paradigm detection to facilitate therapy and diagnosis of emotion regulation in BD[114].

Therapeutic approaches to ED[13]

Currently, new therapeutic approaches are being researched, in particular, some methods inherent in the main mood disorders (borderline, major depressive and bipolar disorder) will be taken up in the paragraphs dedicated to them (2.4 Emotional dysregulation in mental disorders).

In the last years, cognitive behavioral therapy has progressively adopted an interactive-ontogenetic approach to explicate the development of disorders associated to emotional dysregulation. Nevertheless, standard Cognitive Behavior Therapy (CBT) methods are not always beneficial in treating emotional dysregulation. A new CBT-derived tactic named Schema Therapy (ST), that integrates theory and techniques from psychodynamic and emotion-based therapy, aims to bring clarity on this theme. This psychopathology model focus on the interaction between the innate temperament of the child and the early experiences of deprivation or frustration of the subject's basic needs. Its theory believes that deprivation may lead to develop early maladaptive schemas (EMS), and maladaptive modes. Thanks to a special attention on the therapeutic relationship and emotion focused-experiential techniques, this approach successfully treats severe emotional dysregulation.[46]

2.4 Emotional dysregulation in mental disorders

Emotion dysregulation can be related with an experience of early psychological trauma, brain damage, or chronic, and related illnesses such like attachment disorder [2].

Additionally, emotional dysregulation is present in a wide variety of mental illnesses such as attention deficit hyperactivity disorder,[3] autism spectrum disorders, bipolar disorder, borderline personality disorder, complex post-traumatic stress disorder, and fetal alcohol spectrum disorders. [4, 5, 6] In such situations as borderline personality disorder and complicated post-traumatic stress disorder,[7] hypersensitivity to emotional stimuli produces a longer recovery to a normal emotional state. This is indicated physiologically by deficits in the frontal cortices. [8]

Literature stated that in many mental disorders, such as ADHD, psychosis, or affective mood disorders, ED is an essential but often ignored part of psychopathology, with a relevant role in the progression and maintenance of the symptomatology; in BD it is responsible of reinforcing mood instability and is correlated to impulsive behaviors, as well as an increased risk of suicidality [35]. Meanwhile in BPD patients ED is the strongest predictor of impulsivity and self-harm over time. Both BD and Schizophrenia patients have also revealed difficulties into regulating emotions during episodes and remission [35]. Also, in Schizophrenia it appears to be related to both positive and negative symptoms. Finally, talking about neurodevelopmental disorders such as ASD and ADHD, ED seems to be a cofactor for most of the externalizing and internalizing behaviors, specifically in adults. Even PTSD, unrelatedly of the kind of trauma that generates it, is knowingly branded by a general dysregulation of emotions, giving rise to hyper-vigilance, hyper-excitement, emotional numbness, and irritability.

With these premises, can be confirmed the primary tole that ED has as trans-diagnostic risk factor for multiple disorders and symptoms, especially the ones concerning internalizing problems. In this review, it will be often emphasized both the importance of conducting an attentive valuation of the strategies of emotional

regulation during the diagnostical process and the therapeutic central position that it occupies [35].

A psychopathological role of ED in mental illnesses

Infants at familial high risk of severe mental illness have a markedly probability of various psychopathology and constitute a group at significant risk of emotion regulation problems.

With the aim of investigating a possible pathogenetic role of emotional dysregulation in the onset of mental disorders a study has applied an instrument for assessing emotion regulation, the Tangram Emotion Coding Manual (TEC-M), to a sample of 522 7-year-old children born to parents diagnosed with either schizophrenia or bipolar disorder and matched controls. The TEC-M is an ecologically valid, clinician-rated observational test measure of spontaneous emotion regulation marking emotion regulation between risk groups and to investigating possible associations between emotion regulation, psychopathology, and daily life functioning, and among emotion regulation and an acknowledged questionnaire-based dysregulation profile.

Initially, no differences were found between groups in emotion regulation, while a significant but weak negative association between emotion regulation and both child psychopathology, besides a weak positive association between a dysregulation profile on the Child Behavior Checklist and emotion regulation and current level of functioning.

These results contribute to the comprehending of emotion regulation in familial high-risk children, although additional studies of emotion regulation in children at familial high risk of severe mental illness are necessary[213].

In the following paragraphs the subject of ED in mental disorders will be deepened; while such correlation will be only briefly discussed in Borderline Personality Disorder, the study will widely focus on the association among ED and bipolar disorder, ultimately comparing the previous literature published on the matter with the results of our study.

2.5 EMOTION DYS-REGULATION IN BPD

Borderline personality disorder (BPD) is a mental illness described by long-term patterns of emotional instability, unstable relationships, low self-esteem, and a distorted self-image. People with BPD are characterized by impulsive and dangerous behaviors such as driving recklessly, unsafe sexual activities, eating disorders, and substance abuse [3]. Ten percent of individuals diagnosed with BPD commit suicide [4]. It was approximate that one to two percent of the general population is susceptible to BPD, but a study in 2008 found a lifetime incidence of 5.9% [5,6]. Women are three times more affected than men [7] and make more suicide attempts; nevertheless, men have a greater death rate due to suicide [4][64].

BPD is a serious mental disorder caused, partly, from a malfunction of the emotion control system. From this assumption, the emotion dysregulation is believed to be a basic component of BPD [47] and should be central in clinical observation.

Clinical manifestation of ED on BPD

Social abilities impairment

A recent meta-analysis discloses severe disturbance in social processing components, including a reduced ability to distinguish facial expressions and infer the mental states in BPD. Besides, those with BPD exhibited a strong ostracism response to social interactions succeeded by a perceived social exclusion[352].

Additionally, another recent study detected deficiencies of empathy (cognitive, or emotional) and social cognition in people with BPD. These elements might serve

to postpone the creation of secure interpersonal connections and perpetuate dysfunctional social functioning in BPD.

Interpersonal issues and struggle in processing social information in BPD can be related to patients' maladaptive meta-social cognitive style and top-down repercussions of these anomalies rather than having a core social cognitive impairment[353].

Emotional regulation strategies

BPD is associated with a limited use of ER strategies that could be more effective at reducing negative thoughts (i.e., cognitive reevaluation, problem solving, and acceptance) and more a frequent reliance on ER strategies considered less helpful in reducing negative affect (i.e., suppression, rumination, and avoidance).

When compared to those with other mental illnesses, people with BPD indicated higher rates of rumination and avoidance, and less difficulties in applying a problem-solving approach and acceptance[49].

A meta-analysis reveals a difficulty in selecting more successful ER tactics over ineffective ones in BPD, potentially restricting the success of ER attempts in the short term and perpetuating emotion dysregulation in the long run [47].

Impulsivity

Impulsivity and ED are central and important features in BPD. As debated by Sebastian et al., the typical impulsivity in BPD (if not caused by ADHD) could be just another dependent and secondary element of ED; Besides, impulsivity is deeply related with suicide attempts in both adults and adolescents and non-suicidal self–injury, whether it is planned or not. In the meantime, ED is believed to be the strongest predictor of self-harm in the long term and serves as a maladaptive strategy to reduce negative affect and to regulate the mood.

Other analyses have chosen to focus on the role of ED in determining aggressive behavior and behavioral dyscontrol in BPD [35].

On a more detailed note, ED in BPD patients often manifests through these typically observed behaviors:

- *Rapid Mood Swings and Irritability*: BPD patients often struggle to manage moods and expressing emotions, leading to anxiety and irritability. Mood swings may be intense as well as rapid. These feelings may interfere with normal activities. Emotional reactivity could be the principal factor causing this phenomenon. Patients with this condition tend to react quickly and intensely to the situations they encounter.

- *Difficulty Controlling Anger*: BDP patients are not usual to episodes of intense anger, seemingly out of nowhere, sometimes triggered by minimal inconveniences and potentially leading to destructive or violent behaviors, including self-harm.

- *Feelings of Emptiness*: a perpetual sense of emptiness has been often described by BDP patients. Even if its origin is yet not completely clear it may be related to an insecure self-image. In fact, BPD is often correlated with the lack of a secure sense of identity, leading to dissociation from reality. This occurrence may lead to impulsive behaviors, as well as self-harm and suicide, in addition to making the maintenance of interpersonal relationships and emotion regulation more difficult.

- *Paranoia and Fear of Abandonment*: people with BPD are often afraid of being left alone, rejected, or abandoned by those closest to them. This can cause intense paranoia and may bring them to act obsessively and constantly seek reassurance, or even to push others away to avoid feeling hurt by a future rejection[100].

Diagnosis

In spite of being the most significantly investigated personality disorder, its diagnosis is still quite challenging. BPD can be theorized as a severe mental disorder that persists over time with changing manifestations. Age-related symptoms should be considered in the diagnosis, perhaps focusing the treatment on ED and impulsive behavior in youngster. The reason behind this is due to the greater prevalence of anger and self-injurious behavior among younger BPD patients, while older manifest a higher occurrence of alterations in emotion social functioning.

Treatment

The focusing of the treatment should be able to improve patients' relationships. As claimed in the study conducted by Peter et al., a therapy based on teaching how to manage and understand emotions contributes to a considerable improvement in the psychopathological picture. For this reason, implementing specific treatment practice such as dialectical behavior therapy (DBT) could reveal beneficial[35].

2.6 EMOTION DYS-REGULATION IN BD

Our study aims to analyze as fully as possible the relationship between emotional dysregulation and bipolar disorder. With this proposal it has been attempted to report, in the broadest way, all the studies concerning the subject published so far. This in order to compare them with the results of our study and identify possible new fields of research.

In this regard, it is particularly useful a recent systematic review and meta-analysis published in 2022, which reviewed those original studies providing quantitative data on ER and/or ED, assessed with a validated scale, in BD patients and

compared with non-clinical groups (HCs or FDRs) systematically searching the PubMed/MEDLINE, EMBASE, Scopus, and PsycINFO databases from inception until November 25, 2021. This, with the intention of outlining and quantifying which ER strategies or ED features, measured with an objective validated tool, allow differentiating individuals with BD from non-clinical populations such as HCs or their unaffected first-degree relatives (FDRs) (M. De Prisco et al. Neuroscience and Biobehavioral Reviews, 2022). The study was interrupted at the end of 2021, therefore the publications of the last two years containing data conforming to the objective of our study were integrated, so as to collect an updated pool of quantitative values obtained through sensitive tests for emotional dysregulation in bipolar patients, in order to be in a position to make a truthful comparison, highlighting possible new correlations or strengthening those already identified. Recent articles related to the topic have also been integrated, although not strictly focused on the quantitative scales of emotional dysregulation.

Despite the significant results obtained by these recent publications, it should be emphasized that these studies are not without limitations. First, the present meta-analysis written by De Prisco et all. presented an inadequate number of studies included, therefore it was not possible to perform meta-regressions to study the impact of continuous variables (i.e., mean age, percentage of females among the populations, fraction of people in a particular mood state) on the global effect size. Second, several of the explored differences were considerable, but this could be due to the use of self-report questionnaires. Even if the current review focused on those instruments because of their clinical relevance, lower effect sizes when exploring the topic with hetero-reported valuation could be reasonably expected. Third, trial sizes differed much across the comparisons and were small in general, advising the need to further studies on the matter.

Correlation between BD and ED in literature

People diagnosed with BD have regular emotional fluctuations and spend long time being symptomatic experiencing major acute or minor affective episodes. Such conditions encourage these individuals to develop a series of strategies that are part of the process of emotion regulation (ER), aimed at controlling their emotional state[51]. Patients with BD show greater ED when compared to healthy controls, with a bigger overall difficulty regulating emotions [35], both at an explicit level, purposeful, and at an implicit level, automatic and unconscious[181, 354, 355].

Early life traumas, personality traits, or neurobiological components may impact the ER abilities in patients with BD, who are consequently particularly vulnerable to ED. Additionally, they may display alterations in cortical (prefrontal and orbitofrontal cortex) and subcortical (amygdala and hypothalamus) brain regions that are responsible of emotional perception, integration, and its behavioral translation [51].

Clinical manifestation of ED in BD

The studies included in the meta-analysis, twelve of them (Becerra et al., 2016, Carruthers et al., 2022, Das et al., 2014, Ives-Deliperi et al., 2013, Linke et al., 2020, Musket et al., 2021, Oh et al., 2019, Oymak Yenilmez et al., 2021, Palagini et al., 2019, Sağlam et al., 2020, Van Rheenen et al., 2020, Van Rheenen et al., 2015) used the DERS (Gratz and Roemer, 2004), seven studies (Fletcher et al., 2013, Green et al., 2011, Hassani and Kia, 2016, Kanske et al., 2015, Lois et al., 2017, Rowland et al., 2013, Wolkenstein et al., 2014) adopted the CERQ (Garnefski and Kraaij, 2007), six studies (Edge et al., 2013, Fletcher et al., 2013, Johnson et al., 2016, Peckham et al., 2016, Shapero et al., 2015, Weinstock et al., 2018) utilized the RPA (Feldman et al., 2008), four studies (Aslan and Baldwin, 2021, Johnson et al., 2016, Oh et al., 2019, Zhang et al., 2018) used the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003), four studies

(Aslan and Baldwin, 2021, Oh et al., 2019, Peckham et al., 2016, Shapero et al., 2015) used the Ruminative Response Scale (RRS) (Treynor et al., 2003), and four studies (Fletcher et al., 2013, Perich et al., 2011, Van der Gucht et al., 2009, Weinstock et al., 2018) adopted the Response Style Questionnaire (RSQ) (Nolen-Hoeksema, 1991).

An overall of 9 cross-sectional studies (Becerra et al., 2016, Das et al., 2014, Linke et al., 2020, Musket et al., 2021, Oh et al., 2019, Oymak Yenilmez et al., 2021, Palagini et al., 2019, Sağlam et al., 2020, Van Rheenen et al., 2020) and 1 prospective-cohort study (Ives-Deliperi et al., 2013) comprehending 472 BD patients and 415 HCs explored the overall imparments in ER among these categories. Five studies (Becerra et al., 2016, Das et al., 2014, Oh et al., 2019, Oymak Yenilmez et al., 2021, Van Rheenen et al., 2020) comprised only people in euthymia, one study (Palagini et al., 2019) included only depressed patients, and four studies (Ives-Deliperi et al., 2013, Linke et al., 2020, Musket et al., 2021, Sağlam et al., 2020) was constituted by a majority of euthymic patients along with others who were depressed or manic.

From a clinical point of view, ED may aggravate the severity of manic symptoms and residual depressive symptoms (Rucklidge, 2006). Moreover, BD subjects may display ED in euthymia, as they also are likely to adopt maladaptive ER strategies (Dodd et al., 2019), and present more difficulties in moderating positive emotions (Gruber, 2011) compared with healthy controls (HCs). Due to its relationship with sleep disorders, circadian rhythmicity, and suicidality (Palagini et al., 2019), ED could worsen the clinical progression of BD, affect psychosocial functioning (Van Rheenen and Rossell, 2014), and quality of life (Hoertnagl et al., 2011), henceforth requiring particular treatment strategies (Dadomo et al., 2016). Accordingly, an ED assessment in BD is fundamental considering that it is a core feature of BD, and that ER holds the potential of being a target of personalized interventions.

Regrettably, an univocal and shared definition of ED does not yet exists (D'Agostino et al., 2017), and a comprehensive view on this issue is challenging (Shaw et al., 2014). On this matter, numerous tools were elaborated providing a

focus on specific aspects of ED, such as the Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski and Kraaij, 2007), the Response to Positive Affect (RPA) scale (Feldman et al., 2008) and the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004).

According with what is believed to be the first meta-analysis providing quantitative evidence of differences in emotional regulation strategies between patients with BD and healthy controls, as well as between patients with BD and those affected by BPD, published by A. Miola, BD patients presented significantly higher "total" scores (SMD=0.88; Q test $p = 0.23$) at DERS and observing the prediction intervals the comparison remained significant. By leading sensitivity analyses, removing any of the studies did not change the significance and the direction of the comparison. The study counting total of 3 cross-sectional studies (Linke et al., 2020, Sağlam et al., 2020, Van Rheenen et al., 2020) including 145 BD patients and 142 unaffected FDRs examined the general difficulties in ER among these categories. One study (Van Rheenen et al., 2020) included only people in euthymia, and two studies (Linke et al., 2020, Sağlam et al., 2020) included a majority of euthymic patients together with others who were depressed or manic.

BD subjects presented only people in euthymia presented a lower effect size than those considering people in any mood state. Analyzing the GOSH plots, subsets including the Van Rheenen 2020 study appeared to present higher heterogeneity and lower effects size than those that did not.

Studies whose population was totally (Palagini et al., 2019) or partly (Sağlam et al., 2020) depressed had a higher effect size than those considering people in euthymia; compared with the latter, the study (Musket et al., 2021) with the highest percentage of manic patients had a lower SMD instead. Observing the GOSH plots, subsets including the Linke 2020 or Ives-Deliperi 2013 studies showed higher heterogeneity and higher or lower effect size, respectively.

In conclusion, the present systematic review and meta-analysis aimed at describing which ER strategies and ED features are typical of people diagnosed with BD in compared with the non-clinical populations. People with BD engage more maladaptive ER strategies when compared to HCs. This difference is maintained when compared to unaffected FDRs, even if it appears to be lower.

On a more precise note, BD patients exhibit limited access to ER strategies and an excessive focus on negative aspects of life when compared to HCs, anticipating catastrophic consequences, and blaming themselves or others of things that happen in their life. As proposed by another study focusing on the same population (Nitzburg et al., 2016), the struggles experienced by these patients in the early phases of the illness can lead to negative experiences, which could trigger discouragement and self-criticism. In sequence, self-blame appears to be associated with lower real-world functioning, resulting in a worsening of BD.

A higher likelihood to ruminate was experienced in BD. This discovery is important considering the role that rumination might have on the onset of dysregulated behaviors or poor sleep quality (Watkins and Roberts, 2020), possibly worsening the course of illness (Alloy et al., 2017). Furthermore, rumination affects with concentration, problem-solving or goal-directed activities (Watkins and Roberts, 2020), which is consistent with the higher scores obtained in specific subscales of the DERS.

BD patients were more likely to engage risky or impulsive behaviors in response to negative emotions that are experienced as overwhelming and out of control. This is coherent with existing literature exploring this relationship through neurocognitive tests (Ramírez-Martín et al., 2020). Certainly, impulsivity is common in individuals with BD and affective patients within the BD spectrum (Furio et al., 2021), and it is associated with poorer clinical prognosis (Etain et al., 2013) and higher suicide risk (Jiménez et al., 2016). Even though these aspects seem to be common to all BD patients, the affective state may play a role on them. Actually, the high impulsivity observed in euthymic individuals appears to be even more noticeable in samples with a higher proportion of depressed and manic patients, even though it may stand on different theoretical grounds. Impulsive

behavior in the manic patient may be driven by motor-like impulsivity combined with an incapability to delay a reward-related response. Then again, in the depressed patient it may occur as an attentional or no-planning impulsivity that seems to be related to hopelessness and anhedonia (Swann et al., 2008).

Suppression among people with BD was commonly approached. A possible explanation of this manifestation might be the existence of alterations in several brain areas, such as the prefrontal cortex and amygdala, that were also associated with expressive suppression in neuroimaging studies (Cutuli, 2014). Depressive symptoms might also play an important role, and the review found that depressed patients made higher use of this ER strategy. Cognitive impairments are often associated with depression (Richardson and Adams, 2018) and may make it difficult to adopt some adaptive ER strategies, encouraging the use of suppression as an alternative way to ward off an unpleasant emotional state (Dryman and Heimberg, 2018). Nevertheless, due to the small effect size of the comparison and the wideness of the prediction intervals, further research in needed to clarify to which extent BD patients differ from HCs in containing their feelings.

Considering instead the adaptive ER strategies, an opposite trend emerges. Nevertheless, the notion that BD subjects are less prone to positively reframe an experience or be able to distract themselves by initiating amusing activities should be taken with carefulness, since the prediction intervals crossed the null value in most of these findings. Equally, the extent to which these populations differ in terms of acceptance of experienced negative emotions is debatable. Mood state might partly clarify this issue since our results showed that depressed BD patients felt more embarrassed, angry, guilty, ashamed, or irritated when they got upset. Nevertheless, research conducted only on depressed patients addressing the acceptance were not found, which limits the observations on this topic.

Past evidence recommends that BD patients are more likely to calm down their own positive emotions than to amplify them. BD strongly impacts patients' and their families' lives, leaving them with feelings of guilt, shame, or regret their actions occurred during an acute mood episode (Granek et al., 2016), and numbing

positive feelings may be interpreted as a personal strategy to cope with manic or hypomanic symptomatology (Edge et al., 2013). Perhaps for the same reason, studies including only BD-I patients presented a greater effect size in this comparison, and among the others, the lowest effect was carried by the study which comprised the smallest percentage of patients with BD-I (Shapero et al., 2015). Remarkably, the study that comprehend only depressed subjects had the highest effect size, and the reason may be due to the scale used to measure this aspect. In fact, some of the items (Feldman et al., 2008) that form the "dampening" subscale of the RPA recall negative and catastrophic thoughts, so patients with lower mood may be more prone to give higher scores to these specific items.

To put it briefly, people diagnosed with bipolar disorder display high levels of emotion dysregulation that affects the global functioning and quality of life. Among the maladaptive regulation strategies, negative focus, rumination, and risk-taking behaviors are the most recurrent, whilst the evidence regarding the adaptive strategies is uncertain. First-degree relatives present similar modifications compared to fully syndromic individuals, suggesting that emotion dysregulations may be partly heritable, but further research on the topic extended to broader populations is needed.

Maladaptive and adaptive strategies will now be analyzed more specifically.

2.7 Maladaptive emotion regulation strategies in BD

Negative rumination

An overall of 13 cross-sectional studies including 855 BD patients and 804 HCs examined the extent of negative rumination among these categories. Precisely, 6 studies (Green et al., 2011, Hassani and Kia, 2016, Kanske et al., 2015, Lois et al.,

2017, Rowland et al., 2013, Wolkenstein et al., 2014) adopted the CERQ, 4 studies (Aslan and Baldwin, 2021, Oh et al., 2019, Peckham et al., 2016, Shapero et al., 2015) utilized the RRS, 2 studies (Perich et al., 2011, Van der Gucht et al., 2009) the RSQ, and 1 study (Fletcher et al., 2013) used both the CERQ and the RSQ. Six studies (Kanske et al., 2015, Lois et al., 2017, Oh et al., 2019, Peckham et al., 2016, Shapero et al., 2015, Wolkenstein et al., 2014) incorporated only people in euthymia, one study (Aslan and Baldwin, 2021) included only depressed patients, and two studies (Perich et al., 2011, Van der Gucht et al., 2009) included a majority of euthymic patients together with others who were depressed or manic.

BD patients significantly differed from HCs in all the evaluations, with higher scores at the "rumination" subscale of the CERQ (SMD=0.95; Q test $p = 0.43$), at the "brooding" (SMD=0.8; Q test $p < 0.01$), and "reflective pondering" subscales of the RRS (SMD=0.81; Q test $p < 0.01$), and at the "rumination" subscale of the RSQ (SMD=1.85; Q test $p < 0.01$). Observing the prediction intervals, all these assessments remained significant aside for the ones relative to the RRS. Considering only good-quality studies, the assessments remained significant, and the studies adopting the RRS presented a lower but more precise effect size. Subgroup analysis displayed that at the "brooding" subscale, the ones including only people in euthymia showed a lower effect size compared to the one including people in any mood state, and this difference was significant. The same was detected when considering the "reflective pondering" subscale. Single studies whose sample was entirely (Kanske et al., 2015, Lois et al., 2017, Wolkenstein et al., 2014) or almost entirely (Perich et al., 2011) euthymic showed higher effect sizes than the others at the "rumination" subscale of the CERQ and of the RSQ, respectively. Observing the GOSH plots, subsets including the Fletcher 2013 study seemed to present higher heterogeneity and effect size in the comparison relative to the "rumination" subscale of the CERQ, while subsets including the Aslan 2021 study seemed to present higher heterogeneity and effect size in the comparison relative to the "brooding" subscale.

An overall of 2 cross-sectional studies (Green et al., 2011, Kanske et al., 2015) including 127 BD patients and 141 unaffected FDRs examined the extent of

negative rumination among these groups. One study (Kanske et al., 2015) included only people in euthymia.

BD patients presented significantly higher scores at the “rumination” subscale of the CERQ (SMD=0.82; Q test p = 0.17) and observing the prediction intervals the comparison remained significant. The single study that included only people during euthymia had a higher effect size than the other.

Positive rumination

An overall of 3 cross-sectional (Fletcher et al., 2013, Shapero et al., 2015, Weinstock et al., 2018) and 1 prospective-cohort study (Johnson et al., 2016) including 321 BD patients and 406 HCs explored the examined the positive rumination between these categories. One study (Shapero et al., 2015) incorporated only people in euthymia, and one study (Weinstock et al., 2018) only depressed patients.

BD subjects displayed significantly higher scores at the “emotion-focus” subscales of the RPA scale (SMD=0.37; Q test p = 0.13). Observing the prediction intervals, the comparison became not significant. Even with additional sensitivity analysis, removing any of the studies from the comparison relative to the “emotion-focus” subscales did not change its significance or direction, while removing the Fletcher 2013 study from the comparison relative to the “self-focus” subscale the overall effect became significant. Single studies including only euthymic or depressed patients presented similar effect sizes in both the evaluations. Observing the GOSH plots, subgroups including the Fletcher K 2013 study seemed to present higher heterogeneity and lower effect size in the comparison relative to the “self-focus” subscale.

Negative focus

An overall of 6 cross-sectional studies (Fletcher et al., 2013, Green et al., 2011, Hassani and Kia, 2016, Kanske et al., 2015, Rowland et al.,

2013, Wolkenstein et al., 2014) comprising 484 BD patients and 320 HCs examined the extent of negative focus between these groups. Two studies (Kanske et al., 2015, Wolkenstein et al., 2014) included only people in euthymia.

BD subjects displayed significantly higher scores at the “self-blame” (Q test p = 0.05), “blaming others” (p = 0.59), and “catastrophizing” subscales of the CERQ (p = 0.02). Observing the prediction intervals, all the assessments remained significant. Additional sensitivity analyses, even removing any of the studies, or considering just good-quality ones did not change the significance and the direction of the comparisons. Subgroup analysis stated that among the meta-analyses with noteworthy heterogeneity, the studies including only people BD-I patients showed a lower effect size and reduced heterogeneity than the ones including people diagnosed with any type of BD. As an alternative, studies that included only people in euthymia had a higher effect size when compared with the others, but this difference was not significant. By inspecting the GOSH plots, subsets including the Fletcher2013 study seemed to present, in all the previous evaluations, higher heterogeneity and effect size.

A total of 2 cross-sectional studies (Green et al., 2011, Kanske et al., 2015) including 127 patients diagnosed with BD and 141 unaffected FDRs explored the extent of negative focus among these groups.

BD patients displayed significantly greater scores at the “self-blame (p = 0.06), and “catastrophizing” subscales of the CERQ (p = 0.71). Observing the prediction intervals, the comparison relative to the “self-blame” subscale revealed not significant. The single study that included only people in euthymia had a higher effect size than the other in the comparisons relative to the “self-blame” and “catastrophizing” subscales.

Risk-taking behavior

An overall of 13 cross-sectional studies containing 870 BD patients and 647 HCs examined the extent of risk-taking or impulsive behaviors between these groups. Precisely, 10 studies (Becerra et al., 2016, Carruthers et al., 2022, Das et al.,

2014, Linke et al., 2020, Musket et al., 2021, Oh et al., 2019, Oymak Yenilmez et al., 2021, Sağlam et al., 2020, Van Rheenen et al., 2020, Van Rheenen et al., 2015) utilized the DERS, and 3 studies (Fletcher et al., 2013, Perich et al., 2011, Van der Gucht et al., 2009) adopted the RSQ. Five studies (Becerra et al., 2016, Das et al., 2014, Oh et al., 2019, Oymak Yenilmez et al., 2021, Van Rheenen et al., 2020) comprised only people in euthymia, and seven studies (Carruthers et al., 2022, Linke et al., 2020, Musket et al., 2021, Perich et al., 2011, Sağlam et al., 2020, Van der Gucht et al., 2009, Van Rheenen et al., 2015) included a majority of euthymic patients along with others who were depressed or manic.

BD subjects presented substantially greater scores at the “impulse” subscale of the DERS ($p < 0.01$), and at the “risk-taking” subscale of the RSQ ($p = 0.14$). Observing the prediction intervals, the assessments remained significant. Further sensitivity analyses removed any of the studies, or considered just good-quality ones and the significance and the direction of the comparisons remained the same.

Subgroup analysis showed that among the studies exploring the differences in the “impulse” subscale studies containing only people in euthymia presented a lower effect size than the ones including people in any mood state. In the same evaluation, both studies including the highest percentage of depressed (Van Rheenen et al., 2015) or manic (Musket et al., 2021) patients had a higher effect size than those that considered people in euthymia. By inspecting the GOSH plots, subsets including the Linke 2020 study presented higher heterogeneity and effect size in the comparison relative to the “impulse” subscale.

A total of 3 cross-sectional studies (Linke et al., 2020, Sağlam et al., 2020, Van Rheenen et al., 2020) including 145 patients diagnosed with BD and 142 unaffected FDRs examined the extent of risk-taking or impulsive behaviors between these groups. One study (Van Rheenen et al., 2020) included only patients in euthymia, while the others included a majority of euthymic patients together with others who were depressed or manic.

BD patients presented significantly greater scores at the “impulse” subscale of the DERS ($p = 0.12$). Observing the prediction intervals, the assessment remained

significant. Additional sensitivity analyses, removing any of the studies did not change its significance or direction. The single study that included only people in euthymia had a lower effect size than the others who did not. By inspecting the GOSH plots, subsets including the Linke 2020 study seemed to present higher heterogeneity and effect size[51].

Suicidality

Two particular studies aimed to evaluate the difficulties in emotion regulation in schizophrenia (SZ) and bipolar disorder patients and their relationship with suicidality, aggression, and impulsivity.

The results shown than in patients with bipolar disorder (n=85) the scores of DERS, Barratt Impulsivity Scale (BIS-11), Suicidal ideation, Suicide behavior scores, Suicide Probability Scale (SPS), and Buss-Perry Aggression Questionnaire (BPAQ) were significantly correlated. DERS scores of patients with BD and SZ were higher than healthy individuals, while DERS score Total and BIS Total scores of bipolar patients with suicide attempts were significantly higher than bipolar patients with suicidal ideation and bipolar patients with neither attempt nor ideation[120].

Also, the motor and total scores of the Barratt Impulsivity Scale (BIS-11) were higher in patients with BD than in patients with SZ and healthy individuals. According to Spearman correlation analysis, a significant positive relationship was found between all subscales of DERS and all subscales of SPS; physical aggression, anger, and hostility subscales of BPAQ; attention and motor subscales of BIS-11 [34].

According to the hierarchical regression analysis, strategies, clarity, and non-planning impulsiveness were found as the predictors of suicidal ideation in bipolar patients[120]-

These results show that suicidal behavior has a significant relationship between emotional dysregulation and impulsivity in patients with BD and that suicidality may increase in patients with schizophrenia and bipolar disorder who have

difficulty in emotion regulation[34]. Researchers must cautiously evaluate emotional dysregulation and impulsivity among this population to develop treatment strategies in suicide prevention [106].

Differentiating impulsivity from aggressivity

Elevated aggression and impulsivity are implicated in bipolar disorder; however, relationships between these behavioral constructs have not been clarified, which can lead to misinterpreting impulsivity and aggression as the same characteristic with negative consequences including stigma and adverse outcomes including suicide. In fact, in most cases impulsivity in bipolar patients manifests itself in the form of self-harm, rather than aggression towards others. Unfortunately, most sensitive scales for impulsivity do not distinguish the directionality of patients' harmful behaviors.

For this reason, a study has proposed to clarify this misconception, with the attempt to identify brain-based distinctions between the two terms and their associations to risk factors, symptoms and suicide thoughts and behaviors and detecting which were the impulsive attitudes actually undertaken by bipolar patients.

The study also aims to investigate a possible correlation between impulsivity and childhood maltreatment (CM), particularly emotional CM, depression, substance use disorders (SUDs) and suicide attempts (SAs); besides suggesting the existence of two separable brain-based domains of dysfunction in BD, one located in anterior cingulate cortex and identifiable by GMV decreases, responsible for the motor impulsiveness while the other employed to the development of emotionally dysregulated feelings that are primarily self-directed localized in bilateral orbitofrontal cortex and left posterior insula brain regions and characterized by GMV decreases. Both domains are associated with suicide behavior and modifiable risk factors of CM, depression and SUDs that could be targeted for prevention.

Two rating scales were mainly used: Self-rated Brown-Goodwin Aggression (BGA), which the total score is the sum of scores on ten items, each the maximum of adolescent and adult frequencies (never = 1, rarely = 2, occasionally = 3, often = 4) (Coccaro et al., 1996; Manuck et al., 1998) and Barratt Impulsiveness Scale (BIS), which instead provides measures of cognitive behavior domains of motor, non-planning, and cognitive-attentional impulsiveness. Scores were compared between adults with BD (n = 38, 74% female) and healthy controls (HC, n = 29, 64% female). Relationships were examined between BGA and BIS with childhood trauma questionnaire (CTQ), mood, comorbidities, and magnetic resonance imaging gray matter volume (GMV) assessments**.**

In BD, BGA and BIS total scores were both elevated and associated with childhood maltreatment (CM), particularly emotional CM, depression, substance use disorders (SUDs) and suicide attempts (SAs). BGA scores were increased by items corresponding to dysregulation of emotional and social behavior and associated with elevated mood states and suicide ideation and GMV decreases in bilateral orbitofrontal cortex and left posterior insula brain regions, previously associated with these behaviors and clinical features. BIS motor impulsiveness scores were associated with GMV decreases in anterior cingulate cortex implicated in mood and behavioral loss of control *(figure 6, 7).*

Although these data may be limited by the modest sample size and the presence of self-reports questionnaires, those findings suggest separable brain-based domains of dysfunction in BD of motor impulsiveness versus emotionally dysregulated feelings that are primarily self-directed. Both domains are associated with suicide behavior and modifiable risk factors of CM, depression and SUDs that could be targeted for prevention[55].

Discussing a final relevant study on the subject, has been examined the possible correlations between the relationship between childhood trauma, impulsivity, and dissociative symptomatology with emotional dysregulation in BD with a special focus on the role of impulsivity as a mediator between childhood trauma and dissociative symptomatology.

In bipolar disorder patients, trauma has been correlated with emotional dysregulation, potentially provoking an increase in impulsivity and dissociative symptomatology. The Childhood Trauma Questionnaire (CTQ), Barratt Impulsivity Scale (BIS-11), Dissociative Experience Scale (DES-II), and Alda scale were administered with the aim to verify the hypothesis that impulsivity represented an intervening variable between childhood trauma and dissociation.

The Results proved that CTQ and DES-II scores in 100 BD patients were both significantly related with the quantity of lifetime affective episodes, a clinical course of mania-depression-euthymia, suicidal ideation, a history of antidepressant-induced manic switch, poor responsiveness to mood stabilizers, mixed features, psychotic manifestations, aggressive behavior, and BIS-11 ($p<0.01$). At the regression analysis, CTQ was associated with DES-II ($p<0.001$), while DES-II was associated with the CTQ ($p<0.001$) and BIS-11 ($p< 0.001$), as well as with aggression ($p=0.002$). The mediation analysis proved that impulsivity drastically mediated the effect of childhood trauma on dissociative symptomatology ($z=25.71$; 0.930-1.084).

With these assumptions it is possible to state that Impulsivity might play a key role in onset and prognosis of BD patients. The results may help to increase the knowledge about the possible association among impulsivity, childhood traumatic experiences and dissociative symptomatology. BD patients with dissociative symptoms might profit from a tailored treatment which could include a training based on emotional and behavioral regulation[50].

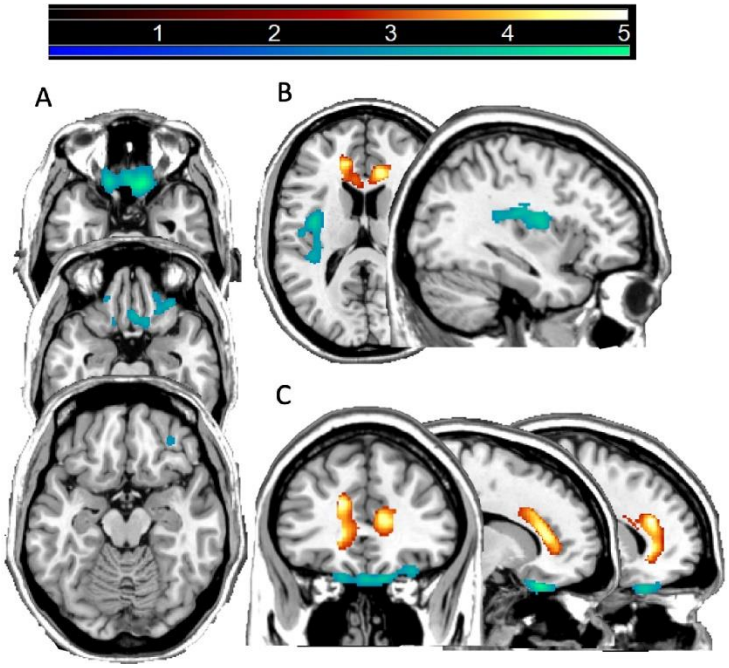

Figure 6 Regions of decreased gray matter volume associated with Brown-Goodwin Aggression and Barratt Impulsiveness Scale scores in bipolar disorder.

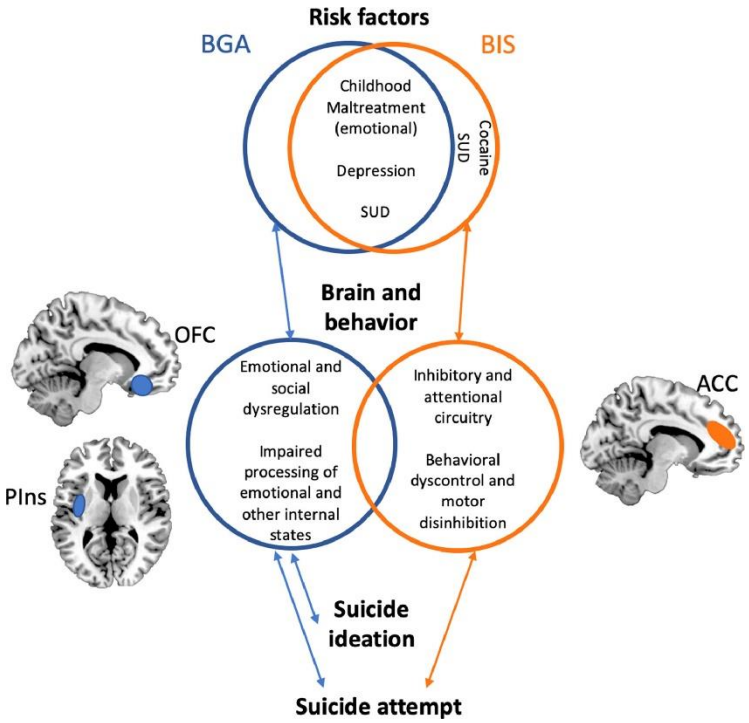

Figure 7 A proposed model of risk, clinical, and brain circuitry features of "aggression" and "impulsivity" in bipolar disorder.

Suppression

An overall of 3 cross-sectional studies (Aslan and Baldwin, 2021, Oh et al., 2019, Zhang et al., 2018) and 1 prospective-cohort study (Johnson et al., 2016)

containing 175 BD patient and 170 HCs surveyed the extent of the suppression between these groups. One study (Oh et al., 2019) included only euthymic patients, while another (Aslan and Baldwin, 2021) solely depressed ones. Finally, one study (Zhang et al., 2018) included both euthymic and depressed patients.

BD patients displayed suggestively higher scores at the "suppression" subscale ($p = 0.25$) of the ERQ, but observing the prediction intervals, the assessment did not remain significant. Further sensitivity analysis removed any of the studies, except for Johnson 2016, and the comparison became not significant. Studies whose sample was entirely (Aslan and Baldwin, 2021) or partly (Zhang et al., 2018) depressed had higher effect sizes than the others.

Dampening

An overall of 5 cross-sectional studies (Edge et al., 2013, Fletcher et al., 2013, Peckham et al., 2016, Shapero et al., 2015, Weinstock et al., 2018) and 1 prospective-cohort study (Johnson et al., 2016) counting 440 BD and 506 HCs examined the extent of the dampening among these categories. Two studies (Peckham et al., 2016, Shapero et al., 2015) incorporated only euthymic patients, and one study (Weinstock et al., 2018) included only depressed patients.

BD patients presented meaningfully increased scores at the "dampening" subscale of the RPA ($p < 0.01$), and observing the prediction intervals, the assessment remained significant. Leading some sensitivity analysis, removing any of the studies from the assessment did not change its significance or direction. Subgroup analysis exposed that the studies comprising only people in euthymia presented a lower effect size than the ones including people in any mood state, and this difference was significant. Moreover, the study (Weinstock et al., 2018) including only depressed patients had the highest effect size between the groups. Observing the GOSH plots, subsets including the Shapero 2015 study appeared to present higher heterogeneity and lower effect size.

2.8 Adaptive emotion regulation strategies in BD

Cognitive reframing

An overall of 9 cross-sectional, and 1 prospective-cohort studies encompassing 659 patients detected with BD and 490 HCs explored the extent of cognitive reframing between these groups. Precisely, 6 studies (Fletcher et al., 2013, Green et al., 2011, Hassani and Kia, 2016, Kanske et al., 2015, Rowland et al., 2013, Wolkenstein et al., 2014) adopted the CERQ, while 4 studies (Aslan and Baldwin, 2021, Johnson et al., 2016, Oh et al., 2019, Zhang et al., 2018) used the ERQ. Three studies (Kanske et al., 2015, Oh et al., 2019, Wolkenstein et al., 2014) incorporated only euthymic patients, one study (Aslan and Baldwin, 2021) included only depressed patients, and one study (Zhang et al., 2018) included both euthymic and depressed patients.

BD patients presented significantly lower scores at the “putting into perspective” ($p < 0.01$), “positive refocusing” ($p < 0.01$), “positive reappraisal” ($p < 0.01$), and “refocus on planning” subscales of the CERQ ($p < 0.01$), and at the “reappraisal” subscale of the ERQ ($p = 0.02$). Observing the prediction intervals, all the assessments became not significant except for the one relative to the “putting into perspective” subscale. performing sensitivity analyses, removing any of the studies did not change the significance and the direction of the assessments, except for the one relative to the “reappraisal” subscale in which removing the Johnson 2016 study made the overall effect not significant. Subgroup analysis showed that among the meta-analyses relative to the “putting into perspective”, “positive refocusing” and “positive reappraisal” subscales, the studies counting only BD-I people presented a lower effect size and smaller heterogeneity, while in the comparison relative to the “reappraisal” subscale, the study comprising only people in euthymia presented a lower and not significant effect size. Revisions including only euthymic patients had respectively lower and higher effect sizes state in the comparisons relative to the “putting into perspective” and “positive reappraisal”, and “positive refocusing” and “refocus on planning” subscales than those considering patients in any mood state: still, these differences were not

significant. Studies whose sample was entirely (Aslan and Baldwin, 2021) or partly (Zhang et al., 2018) depressed had greater effect sizes than the others. By inspecting the GOSH plots, subsets including the Fletcher 2013 study seemed to present in the comparisons relative to "positive refocusing", "positive reappraisal", and "refocus on planning" subscales with higher heterogeneity and effect size than those who did not, while subsets including the Oh 2019 study seemed to present bigger heterogeneity and lower effect size in the comparison relative to the "reappraisal" subscale.

A total of 2 cross-sectional studies (Green et al., 2011, Kanske et al., 2015) including 127 BD patients and 141 unaffected FDRs explored the extent of cognitive reframing among these categories. One study (Kanske et al., 2015) included only people in euthymia.

BD patients presented significantly lower scores at the "putting into perspective" subscale of the CERQ ($p = 0.72$) and observing the prediction intervals the assessment remained significant. The single study that included only people in euthymia had a smaller effect size in the comparison relative to the "putting into perspective" subscale, and a greater one in the comparisons relative to the "positive reappraisal" and "refocus on planning" subscales.

Adaptive coping

A total of 13 cross-sectional studies including 870 patients diagnosed with BD and 647 HCs explored the extent of adaptive coping among these categories. Precisely, 10 studies (Becerra et al., 2016, Carruthers et al., 2022, Das et al., 2014, Linke et al., 2020, Musket et al., 2021, Oh et al., 2019, Oymak Yenilmez et al., 2021, Sağlam et al., 2020, Van Rheenen et al., 2020, Van Rheenen et al., 2015) adopted the DERS, and 3 studies (Fletcher et al., 2013, Perich et al., 2011, Van der Gucht et al., 2009) used the RSQ. Five studies (Becerra et al., 2016, Das et al., 2014, Oh et al., 2019, Oymak Yenilmez et al., 2021, Van Rheenen et al., 2020) included only people in euthymia, and seven studies (Carruthers et al., 2022, Linke et al., 2020, Musket et al., 2021, Perich et al., 2011, Sağlam et al., 2020, Van der Gucht et al., 2009, Van

Rheenen et al., 2015) included a majority of euthymic patients together with others who were depressed or manic.

BD patients reported significantly higher scores at the “goals” ($p < 0.01$), and “strategies” subscales of the DERS ($p < 0.01$), and worse scores at the “adaptive” subscale of the RSQ ($p < 0.01$). Observing at the prediction intervals, these assessments remained significant except for the “adaptive” subscale. Conducting sensitivity analyses, the removal of any of the studies did not alter the significance and the direction of the results, except for the “adaptive” subscale, in which, after the removal of the Perich 2011 study, the overall effect became not significant. Considering only good-quality studies, the comparisons remained significant except for the one relative to the “adaptive” subscale and reported a lower effect size. Subgroup analysis showed that among the studies relative to the “goals” subscale, those including only people in euthymia presented a lower effect size and lower heterogeneity. The same was stated when considering the “strategies” subscale, although this difference was not significant. In both comparisons, studies including the highest percentage of depressed (Van Rheenen et al., 2015) or manic (Musket et al., 2021) patients had a higher effect size than those that considered people in euthymia. Observing the GOSH plots, subsets comprising the Linke 2020 study seemed to present greater heterogeneity and effect size in the comparison relative to the “goals” and “strategies” subscales, while subsets including the Oh 2019 study seemed to present higher heterogeneity and lower effects size in the comparison relative to the “strategies” subscale.

An overall of 3 cross-sectional studies (Linke et al., 2020, Sağlam et al., 2020, Van Rheenen et al., 2020) including 145 BD patients and 142 unaffected FDRs explored the extent of adaptive coping among these groups. The first one (Van Rheenen et al., 2020) sampled only patients in euthymia, while the others included a majority of euthymic patients together with others who were depressed or manic.
BD subjects presented significantly higher scores at the “goals” ($p = 0.25$) and “strategies” subscales of the DERS ($p = 0.09$). Observing the prediction intervals, all these assessments remained significant. After conducting sensitivity analyses,

removing any of the studies did not change the significance and the direction of the comparisons.

Acceptance

A total of 16 cross-sectional studies comprising 964 patients diagnosed with BD and 770 HCs explored the level of acceptance among these groups. Precisely, 10 studies (Becerra et al., 2016, Carruthers et al., 2022, Das et al., 2014, Linke et al., 2020, Musket et al., 2021, Oh et al., 2019, Oymak Yenilmez et al., 2021, Sağlam et al., 2020, Van Rheenen et al., 2020, Van Rheenen et al., 2015) utilized the DERS, while 6 studies (Fletcher et al., 2013, Green et al., 2011, Hassani and Kia, 2016, Kanske et al., 2015, Rowland et al., 2013, Wolkenstein et al., 2014) adopted the CERQ. Seven studies (Becerra et al., 2016, Das et al., 2014, Kanske et al., 2015, Oh et al., 2019, Oymak Yenilmez et al., 2021, Van Rheenen et al., 2020, Wolkenstein et al., 2014) sampled people in euthymia, and five studies (Carruthers et al., 2022, Linke et al., 2020, Musket et al., 2021, Sağlam et al., 2020, Van Rheenen et al., 2015) included a majority of euthymic patients together with others who were depressed or manic.

BD patients demonstrated considerably higher scores at the “acceptance” subscale of the CERQ ($p = 0.74$), and at the “non acceptance” ($p < 0.01$), and “clarity” subscales of the DERS ($p < 0.01$). By looking at the prediction intervals, all these assessments remained significant except for the one linked to the “clarity” subscale. By performing sensitivity analyses, removing any of the studies did not change the significance and the direction of the comparisons, aside for the one relative to the “awareness” subscale in which, by removing Becerra 2016, the overall effect became significant, and to the “acceptance” subscale in which, by removing Fletcher 2013 or Rowland 2013”, the overall effect became not significant. Considering solely good quality researches, the comparisons related to the “acceptance” and “clarity” subscales became not significant. Subgroup analysis indicated that among the studies pertaining to the “clarity” subscale, those including only participants diagnosed with BD-I demonstrated a

considerably smaller effect size and decreased heterogeneity than the ones including people diagnosed with any kind of BD.

Single trials comprising just euthymic individuals revealed lower effect sizes in all these comparisons, and the subgroups substantially varied when looking at the "strategies" subscale. The studies comprising the largest proportion of depressed [204] patients showed a bigger impact size in the comparisons related to "non acceptance" and "strategies" subscales. In contrast, it did not differ in terms of impact magnitude in the comparison relative to the "awareness" subscale. By surveying the GOSH plots, subsets including the Linke 2020 study seemed to present higher heterogeneity and effect size in the comparisons relative to the "non acceptance" and "awareness" subscales; subsets comprehending the Oh 2019 and Becerra 2016 studies seemed to present a bigger heterogeneity and lower effects size in the comparisons relative to the "clarity", and "awareness" subscales, respectively.

A overall of 5 cross-sectional studies (Green et al., 2011, Kanske et al., 2015, Linke et al., 2020, Sağlam et al., 2020, Van Rheenen et al., 2020) counting 272 patients diagnosed with BD and 283 unaffected FDRs examined the extent of acceptance among these groups. Two studies (Kanske et al., 2015, Van Rheenen et al., 2020) included only patients in euthymia, and two studies (Linke et al., 2020, Sağlam et al., 2020) included a majority of euthymic patients together with others who were depressed or manic.

BD patients reported significantly higher scores at the "non acceptance" ($p = 0.1$), and "clarity" subscales of the DERS ($p = 0.34$). Looking at the prediction intervals, all these assessments remained significant. Conducting sensitivity analyses, removing any of the studies did not alter the significance and the direction of the comparisons. The study (Van Rheenen et al., 2020) that included only people in euthymia had lower effect sizes in both comparisons than the others who did not. By inspecting the GOSH plots, subsets including the Linke 2020 study appeared to present higher heterogeneity and effect size in the comparison relative to the "non acceptance" subscale, while subsets including the Van Rheenen 2020 study

seemed to present higher heterogeneity and lower effects size in the comparison relative to the “awareness” subscale[51].

Acceptance: emotional awareness is a fundamental step

An interesting study of this year tried to reach the overall goal to examine the role that trait emotional awareness plays in the association between bipolar spectrum psychopathology, as measured by the HPS, and affective intensity and instability. Importantly, employing a novel method (experience sampling methodology; ESM) and statistical methods (time-series analysis) to assess affect intensity and instability in daily life.

Affective dysregulation is present in those with subsyndromal symptoms of hypomania and mania and prospectively predicts the progress of bipolar spectrum disorders. An important and understudied area regarding the experience and regulation of emotion in this population is emotional awareness - emotional clarity, that is the ability to understand, perceive, and describe their emotions, and attention to emotion, constituting the capacity to, monitor, and value their emotions.

The correlation was examined through the Hypomanic Personality Scale (HPS), a self-report questionnaire elaborated to evaluate dimensional ratings of bipolar spectrum reporting a lifetime history of a hypomanic episode, in which increased scores on the HPS are associated with subclinical and clinical manifestations of mania/hypomania in daily life and predict the development of new cases of bipolar disorders both three and ten years later. It has been established it was actually associated with impairment in emotional awareness and that these deficits were linked with heightened intensity and instability of negative (NA) and positive affect (PA). Young adults (n=233), oversampled for high HPS values completed self-reports as well as 14 days of experience sampling assessing high and low arousal NA and PA.

Clarity and Attention were assessed using the Trait Meta-Mood Scale. Results showed that HPS scores were associated with low Clarity and unassociated with Attention. High HPS scores were related with greater high and low arousal NA intensity and unpredictability only for those at low and mean levels of Attention. As opposite, there was a significant indirect association between HPS scores and intensity of high and low arousal NA and PA, as well as instability of high arousal NA, through low Clarity. Results underlined those individual differences among emotional awareness based on the scores in the HPS to emotional outcomes.

Additional work trying to explain the links between Attention and the experience of emotion propose that their links may be based on the levels of Attention one experiences. The Affect-as-Information theory suggests that the association between affect and judgment should be stronger for those with greater Attention, implying that individuals with low Attention may not value their affective response and are less prone to learn from it. This could potentially indicate that low levels of Attention would be associated with more affective instability. Specifically, they report that the more one attends to positive affects, the more likely they are to ignore mood-incongruent cognitive messaging in an effort to sustain high levels of it. Remarkably, at the momentary level, higher Attention has been linked with greater negative affects concurrently leading initial thoughts that more Attention may be linked with poor emotion regulation; however, higher Attention is predicted decreases the negative affects in a long term [195]. These results underline the possibility that those high in Attention could more successfully down-regulate emotion over time and that the function of Attention at trait vs. state levels and across different timescales may be varied[214].

Emotional dysregulation in bipolar disorder subtypes

Differences between BDI and BDII

An open debate concerns the differences in emotion regulation strategies among BD-I and BD-II within the bipolar spectrum. Studies considering difficulties in emotion regulation in bipolar subtypes, using the DERS scale, revealed no differences in emotion regulation between BD-I and BD-II[162], while De Prisco et all. systematic review attested that People diagnosed with BD-I employed greater adaptive and fewer maladaptive ER strategies than those diagnosed with any BD type. Of the same line of advice appear the words of Fletcher et al. reporting that BP II (but not BP I) patients were more prone to engage in emotion-focused and self-focused rumination about positive affect, in comparison with unipolar depression patients[71]. A particularly important element is the assessment of the sleep pattern in people with BD. In a sample of patients with BD type II diagnosis, the sleep pattern alteration determined emotional alterations that caused an increase in impulsiveness levels, leading to a substantial and statistically relevant augmentation in suicidal behavior. For this reason, a careful assessment and an early intervention on sleep and emotional factor could have a substantial positive impact on the prognosis of the disorder [35].

The difference between the two main types of bipolar disorder are possibly related to the chronic clinical course of BD-II with smaller interval episodes, higher comorbidity occurrence, and less efficient treatment strategies, which could be responsible for partial management of syndromic and subsyndromal symptoms[51].

Finally, research instead documented than in bipolar disorder type II, the dysregulated dimension of emotions in the manic component is less pronounced and tends to be hidden in the euthymic phases of the rest of the population.
Talking about adaptive strategies instead, as announced by Berk, Dodd (2005) and Vieta (2019) seems that BD-I subjects were able to employ more adaptive strategies than the other subtypes of bipolar disorder.

Cyclothymic Disorder

About this matter, it is relevant to notice how numerous studies have identified ED as a nuclear factor of the Cyclothymic Disorder, which is distinguished by a chronic manifestation of low-grade depressive and hypomanic symptoms. Recent studies have emphasized how the Cyclothymic Disorder and the Cyclothymic Temperament are characterized by an increased level of emotional and behavioral instability and over-reactivity. Likewise, the cyclothymic temperament was appeared to be associated with an increased mood and emotional responsiveness, with intense reactions to external stimuli, great irritability, anxiety and scarce impulse control[35].

Role ED in manic and depressive symptoms

The relationship between overall ED and manic or depressive symptomatology remains unclear.

A useful systematic review of this year proposed to examine the correlations between maladaptive (i.e., positive and negative rumination, negative focus, risk taking behaviors, suppression, and dampening) and adaptive (i.e. adaptive coping, cognitive reframing, and acceptance) strategies of emotion regulation (ER) and depressive and manic symptoms of BD.

Both depressive and manic BD symptomatology resulted to be related to maladaptive ER strategies, with the difference that the only manic phases were associated to positive rumination. Negative rumination and risk-taking behaviors meanwhile, most utilized during both manic and depressive symptoms, as confirmed by both pairwise metanalyses and network metanalyses. On the other hand, depressive symptomatology appeared more correlated with decreased adaptive strategies, a marked inhibition of positive emotions and a predilection for negative attitudes and emotions (among which anhedonia and affective flattening dominate) [35] than manic symptomatology. In addition, a longitudinal study of emotion regulation detected that a greater self-reported use of maladaptive emotion regulation strategies predicts depressive symptoms at 6-

months follow-up and more episodes of depression at 3.5-year follow-up [71, 171, 214].

Comorbidity in BD

The role of psychiatric comorbidities is still not sorted out, even though it may drive towards higher values. For instance, in the Linke 2020 study, patients who were comorbid with attention deficit hyperactivity disorder (ADHD) or anxiety disorders, displayed the major difference with HCs. ADHD and anxiety disorders are deeply related to ED, and comorbid samples could be burdened with additional difficulties on their psychopathology.

Due to the degree of cyclothymic temperamental traits in patients diagnosed with BD, or the high prevalence of comorbid borderline personality disorder[74], it is not uncommon find patients with these characteristics. This should be taken into consideration, since more prominent cyclothymic temperaments are regularly related to higher levels of ED and people with BD and comorbid borderline personality disorder often present more difficulties in ER than not comorbid people[21]. Nevertheless, two of the included studies still detected moderate-to-high effect sizes, despite having excluded from their sample people diagnosed with personality disorders, suggesting that other features should be considered to unravel this complex construct[51].

BD patients experiencing euthymia

BD patients experiencing euthymia presented lower ED than patients in any mood state, suggesting that ED in BD might be a trait enhanced by the current mood state. However, it is still unclear whether difficulties in emotion regulation patterns are state-related features in BD, in fact this appears to be in opposition with existing research conducted on different clinical populations (i.e., anorexia nervosa), in which ED appeared to be more a state than a trait feature. Nevertheless, these results were based on a population of patients with very low self-reported depression that could have biased ED self-reports, considering the relationship between ED and depressive symptoms. Similarly, another study

conducted on the same clinical population failed to find a reduction of ED levels sufficient to match those of the HCs, despite the clinical improvement observed. The high frequency of persisting depressive subsyndromal symptoms in people with BD may explain the persistence of moderate-to-high effect sizes observed even among the patients in euthymia [50].

A less neutral conclusion seems to have emerged from the following studies, that seems to have confirmed that ED in the euthymic period is indeed a trait associated with the state of the disease, also related with the severity of symptoms in manic, depressive, and mixed periods [9]. In fact, problems in emotional regulation observed also during phases of symptomatologic remission may lead to worse functional consequences in BD. Actually, deficits in the habitual use of ER strategies are commonly found in BD in euthymic phase and are credited to play a role in the recurrence of mood [46] with an increased incidence of relapses; Furthermore, remitted BD presents significant maladaptive emotion-related impulsivity and tendency to use negative strategies to regulate mood, such as rumination and catastrophizing [35] which is linked with poorer psychosocial functioning and increased manic symptom severity [162].

Comparison with unaffected FDRs

Compared to unaffected FDRs, BD patients exhibited a slighter range of ER strategies and a higher propensity to ruminate or catastrophize. All these remarks presented a lower effect size than the ones related to HCs comparisons, sustaining the hypothesis that FDRs, even if unaffected, present a higher risk for BD. Difficulties in ER could constitute the starting point to establish a measurable correlate of syndromic psychopathological issues. Undeniably, ED seems to fluctuate on a continuum: a dilution of these symptoms occurs from BDs to HCs, and unaffected FDRs lie in between on this gradient. Nevertheless, due to the few included studies exploring these comparisons, further investigation is needed on the subject. The ESM was also used to examine the inter-relationships among mood and ER strategies in a younger FDR of people diagnosed with BD, and the

results were similar to those of clinical populations, although with lower effect sizes. From a clinical point of view, ED could play a tool in prevention programs to reduce the psychopathological burden in individuals with an increased risk of BD (i.e., FDRs)[216].

In conclusion, more studies comprising unaffected FDRs should be conducted to explore the idea that this population may stand on a clinical and neurobiological continuum towards the full threshold BD[51].

Typical characteristics of emotional dysregulation and comparison between bipolar, borderline personality disorder and major depressive disorder

Is bipolar disorder different from other mental illnesses in terms of emotion dysregulation? A systematic review and meta-analysis

ED is familiar in people diagnosed with bipolar disorder (BD), but it can also be detected in other clinical populations given its transdiagnostic nature. Many aspects of ED have been described in BD [51], but it is doubtful whether these manifest equally in other conditions such as major depressive disorder (MDD) or borderline personality disorder (BPD), or whether they are specific to BD.

With this purpose a systematic review and meta-analysis tried to examine the literature comparing BD with other psychiatric disorders in terms of ED, focusing on those studies using validated clinical tools.

Twenty-nine studies were included, and it was possible to perform a meta-analysis with twenty-two (145 comparisons) of them. Only studies comparing BD with MDD, and BPD delivered sufficient data to perform a meta-analysis. In most of the comparison between BD and MDD patients not great differences were detected. Still, BD patients presented higher positive rumination and risk-taking behaviors. BPD patients however, displayed an overall higher level of ED and used fewer adaptive ER strategies. Moreover, higher levels of self-blaming and impulsive behavior were observed[188].

Comparison of ED between BP and BPD patient

Differentiation of the bipolar illness from borderline personality disorder might be problematic owing to overlapping symptoms, with emotional dysregulation being the probable major one[21].

Symptoms of borderline personality disorder and bipolar disorder often overlap. Sometimes, to the point it may be difficult to perform a differential diagnosis based solely on current diagnostic criteria Hence, it is important to find clinical factors with high discriminatory capacity that, paired with structured or semi-structured interviews, could facilitate the diagnostic process.

On several occasions it has been proved that patients with BD and BPD present a greater emotional dysregulation compared to controls, suggesting it may constitute a trans-diagnostic feature. Furthermore, the present study testifies the critical involvement of emotion dysregulation in the functional impairment, which defines the course of BD and BPD. Besides, a recent study of 2022 [162] suggested the presence of a history of childhood trauma in both BD and BPD as an etiological cofactor in the origin of emotional dysregulation.

On a more specifical note, the findings suggest that alterations of specific ER abilities are present in BD and their magnitude is smaller relative to BPD.

A. Miola meta-analysis provided quantitative evidence of differences in emotional regulation strategies among patients with BD and those affected by BPD. In fact, unlike HC, there were no discrepancies in total DERS scores between subjects with BD and those affected by BPD, while subjects with BD showed meaningfully lower scores in all DERS subdomains compared to those with BPD without heterogeneity in the Goals, Impulse and Awareness subdomains among BD and BPD.

Also, were not noticed differences in DERS total scores between patients with BD and those affected by BPD. This results are in line with the difficult differentiation process between the two conditions due to several shared phenomenological features[21, 356]. As formerly reported, patients diagnosed with BD have an higher probability to be diagnosed with BPD compared to those without a diagnosis of BD[357]. Furthermore, patients with BD who suffered a depressive episode with mixed features or those with cyclothymic temperament are inclined to present severe emotional dysregulation and sometimes are misdiagnosed with BPD[179, 199, 358, 359]. Subsequently, meta-analytic evidence shows that the prevalence of BPD among BD is as high as 21.6% [74]. In fact, patients affected by BPD and BD present common clinical features, like emotional dysregulation, mood instability and impulsivity[20, 71]. The diagnostic controversy gave rise to a debate whether these disorders are distinct conditions with shared features, different disorders that heightens the risk of developing the other or part of the same bipolar spectrum[360]. [175, 179, 235, 361]Nevertheless, there are several markers useful in differentiating such conditions, such as a family history of bipolar illness, more commonly detected in patients with BD, while parasuicidal self-harm and a history of sexual abuse are frequently found in BPD[375]. Quoting the words of Ghaemi et al., (2014), the presence of emotional dysregulation as a shared "transdiagnostic" feature may compromise an accurate clinical diagnosis[375]. Coherently, the study showed that, even if subjects with BD presented no differences in DERS total scores compared to BPD, they exhibited inferior scores on all the DERS subscales and in particular in goal-directed behavior, awareness and impulse control, with no high heterogeneity among the groups. These results advocate that, compared to BD, patients with BPD struggle to engage emotion regulation strategies due to impaired emotional awareness that can explain their difficulties in mood labeling previously described[53]. Moreover, BPD exhibited greater difficulties controlling impulsive behaviors and limited access to emotion regulation strategies with a large effect size compared to BD.

The study confirmed the presence of a diminished impulse control in emotional dysregulation in BPD compared to BD. Impaired emotion regulation strategies, as

well as increased impulsivity observed in BPD, can elucidate many of the behavioral problems frequent in this disorder, including high mood unpredictability and deliberate self-harm[116]. Actually, patients affected by BPD displayed a two-fold increased relative risk of parasuicidal self-harm compared to BD [375].

Only one of the studies that estimated DERS scores in BD and BPD described accurately the therapeutic regimens of the participants. It is relevant to note that medications in BD are prescribed both during acute phases and as long-term maintenance treatments[169, 220, 363], while in BPD, pharmacological therapies are usually prescribed for shorter periods and at lower doses compared to BD[17]. Moreover, BPD are less compliant in following the treatments, with higher occurrence of dropouts from both pharmacological and psychological approaches[38, 200]. A variety of international multicentric studies have shown that psychotropic medications, particularly antidepressants, mood stabilizers, and second-generation antipsychotics, are associated with adaptive changes in the strategies used to regulate emotions in affective and mood disorders[23, 105, 135, 156, 175].

Starting from this consideration it would be possible to suspect that better emotion regulation in BD relative to BPD may be partially explained by more appropriate therapeutic interventions in BD compared to BPD. Future research deepening the effect of antidepressants, antipsychotics, and mood stabilizers on emotion dysregulation in these populations are necessary to confirm this hypothesis.

The meta-regression analysis also revealed that age regulates emotional regulation strategies in BD and HC. Equally, sex and sample size seem to moderate the emotional dysregulation differences between BD and BPD, showing a gender-related variance in emotion regulation among these disorders. This finding is coherent with the high prevalence of BPD in women[132].

There are some limitations should be considered when interpreting the results. First, the limited quantity of eligible studies reduced the power of a meta-analysis. Second, the cross-sectional design of the studies and differences in mood states

among participants with BD reduced the capacity to delineate which specific difficulties in emotional regulation characterize mood fluctuations in BD. Third, six studies did not report details on pharmacological treatments, hindering the possibility to explore the potential role of medication in emotion regulation. Finally, the high heterogeneity of the data collected might limit the generalizability of the finding.

In conclusion, the study provided a quantitative measure of emotion dysregulation strategies in BD and BPD, stating that patients with BD present suggestively more difficulties in emotion regulation compared to controls. Additionally, the present work underlines the crucial role of emotion dysregulation in BD and BPD, with a large effect size for the impairment in domains exploring the access to emotion regulation strategies and impulsive behaviors in BPD. More studies, with a prospective longitudinal design, are necessary to better understand whether the impairment profile of emotion regulation strategies is stable over time or depends on the current mood state in BD[162].

In order to facilitate the differential diagnosis between bipolar disorder and borderline disorder, when they are not co-morbid, other studies proposed to investigate clinically identity, self-concept and self-esteem. The reviews emphasize qualitative differences among the two disorders. In BPD, there is a well-documented identity's rupture, and the self-concept appears predominantly negative; shifts in self-concept and self-esteem are often tied to interpersonal triggers. In BD, subjects present impairment with their identity, but narrative identity might be less compromised compared with BPD; the shifts in self-concept and self-esteem seems more linked to internal (mood and motivational) factors. There is an open debate about the implications for clinicians and for its application in future comparative research[123].

2.9 New theories on possible Etiological components responsible for emotional dysregulation in bipolar disorder

1. *The possible role of circadian rhythm alterations in emotion dysregulation on the clinical manifestations of bipolar disorders*

Focusing on the possible role of circadian rhythm alterations in emotion dysregulation on the clinical manifestations of bipolar disorders (BDs) a trial of 197 inpatients suffering from BD of type I (BDI) or II (BDII) were evaluated during a major depressive episode using the Structural Clinical Interview for DSM-5 (SCID-5), the Beck Depression Inventory-II (BDIII), the Young Mania Rating Scale (YMRS), Resilience Scale for Adults (RSA), Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), Difficulties in Emotion Regulation Scale (DERS) and the Scale for Suicide Ideation (SSI). Participants with or without circadian rhythm disorders, measured with Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), were compared; Patients with circadian rhythms instabilities displayed a greater severity of depressive symptoms, of suicidal risk, minor resilience and more disturbances in emotion regulation covering impulsivity and regulatory strategies. The logistic regression showed that circadian rhythm disturbances was associated to depressive symptoms (O.R. 4.0), suicidal risk (OR 2.51), emotion dysregulation (OR 2.28) and low resilience (OR 2.72). At the mediation analyses, circadian rhythm alterations presented an indirect effect on depressive symptoms by impairing resilience ($Z= 3.17$, $p=0.0014$)/ emotional regulation ($Z= 4.36$, $p<0,001$) and on suicidal risk by affecting resilience ($Z= 2.00$, $p=0.045$) and favoring impulsivity ($Z= 2.14$, $p=0.032$).

The current results may suggest that circadian rhythm alterations might play a key role in BD symptoms, as being correlated with a worse clinical presentation of depressive symptoms, suicidal risk, impaired resilience, and emotional regulation. investigating the circadian rhythm alterations might potentially encourage resilience and emotion regulation henceforth improving mood symptoms and suicidal risk in BDs[176].

2. The potential link between BD, ED, and alexithymia

Alexithymia has been characterized as a problem in identifying and expressing emotions[364] and well as predisposing to various mental diseases [365]. Investigations done on patients diagnosed with BD-I, alexithymia scores were often shown to be greater than the control group[68, 80, 298]. In addition, a recent study researched increased alexithymia scores as an estimation of poorer social functioning BD[173]. The same study suggested that alexithymia relates to emotional control strategies such as suppression. Nevertheless, the possible link between alexithymia and ED has yet to be clarified.

Meanwhile it is known that patients with bipolar disorder experience more somatic symptoms than the general population[367]. Somatic symptoms are biological and physical manifestations (like sleep and hunger) that individuals perceive in an uncomfortable or unpleasant way.

A recent study, including 72 bipolar disorder-I patients, used the Difficulties in Emotion Regulation Scale (DERS) to determine the emotional state of the patients, the Toronto Alexithymia Scale to determine the alexithymia scores, and the Somatization Scale for somatization scores[11]. The examination showed that fast cycling was more prevalent in the high-scoring group, and that the illness prognosis in this group was poorer[59].
Permanent ED has been identified in individuals with a diagnosis of somatoform disorder, and investigations are revealing its link with alexithymia[229].

For this reason, it is possible to intuit the existence of deleterious consequences of ED, alexithymia, and somatization on functioning and prognosis in the during course of BD and imply that all these clinical areas may be related to each other. Therefore, recent study hypothesized that higher emotional dysregulation scores might be related to higher alexithymia and somatization severity scores [11].

Having the relations of childhood emotional maltreatment and alexithymia to the clinical course of bipolar disorder (BD) been widely recognized, another study focused on how the difficulties in regulating emotions may explain these relationships. The present article assessed the effects of childhood emotional abuse and alexithymia on depressive and manic symptoms as well as suicidal ideation in female patients with BD. Emotion dysregulation was estimated as a mediating factor.

Three hundred female inpatients with a diagnosis of BD supplied information regarding their history of childhood emotional abuse, alexithymia, difficulties in emotion regulation, depressive and manic symptoms, and suicidal ideation.

The study attested that childhood emotional abuse and difficulty in identifying feelings were indirectly associated with depressive and manic symptoms as well as suicidal ideation. This association was intermediated by emotion dysregulation. The correlation remained significant after depressive and manic symptoms were controlled in the model. For this reason, patients with BD who experienced emotional maltreatment during childhood and struggle to identifying emotions report greater emotional dysregulation. These patients, in turn, are more susceptible to experience more severe depressive and manic symptoms as well as suicidal ideation[112].

3. *Neuroanatomical modifications*

Various empirical studies have established and recognized that BD is a disorder of emotion and motivation. Particularly, the orbitofrontal cortex and the amygdala are implicated and the linking between these two regions is a marker of biological vulnerability in mood disorders[368]. In fact, ED was suggested to be connected not only with negative functional outcomes in BD patients[225] but has also been proposed as a central element in the development and preservation of mood

disorders and reinforcement of mood instability. It also seems to be correlated to impulsive behaviors, and increased risk of suicidality in individuals[35, 85, 94, 96].

Consequently this theme should be deepened to better describe its role in BD neuroprogression[207], advancing the hypothesis that advanced levels of ED may be associated with more severe neuroprogression, and may explain, at least partly, the treatment resistance described [18, 35, 51].

In particular, even if the correlation among BD and emotional dysregulation, as well as the neurobiological bases concerning these conditions, are still poorly comprehended, previous neuroimaging studies like[38, 39, 43, 183, 206, 221, 369] have revealed alterations in brain activity of patients with BD compared to HC in several regions responsible of emotion processing, including the amygdala, insula, thalamus, hippocampus, and prefrontal cortex, and these modifications have been detected in patients with BD during mood episodes, euthymic phases and in individuals at risk for the disorder as well[38, 39, 43, 183, 206, 221, 369]. Deficits in fronto-limbic patterns may provoke difficulties in emotion regulation in BD, constituting both a vulnerability factor for the disorder and a trait biomarker that remains stable across mood states. Future studies addressing the relationship between altered brain structure and functional and emotional dysregulation in BD are needed[162].

Deepening the subject matter a recent research aimed to synthesize the results of functional neuroimaging studies on bipolar patients, and to validate the use of activation maps from our results as a biomarker for BD.

The pathophysiology of BD is complex, but two essential aspects are biochemistry and neuroimaging, which can be used as biomarkers to diagnose and evaluate the disease. Manic and depressive moods seem to be related with alterations in neurotransmitters such as serotonin, which could be responsible for the alteration of volume and activity alterations in some brain regions. Nevertheless, the neuroimaging aspect of BD pathophysiology is connected with specific functional and structural brain fluctuations that are proposed as candidates for biomarkers of this disorder[73].

The most typical impairments of BD are abnormal emotion regulation and elevated emotional reactivity. Functional magnetic resonance imaging (fMRI) studies have been proved useful to investigate functional abnormalities associated with BD using several emotion-regulation tasks[370]. In order to clarify what are the implicit and explicit emotional pathways and which abnormalities have shown to be associated with an imbalance between a functionally hyperactive ventral-limbic pathway and a functionally hypoactive cortical-cognitive pathway[122, 138].
The resolution of this systematic review and meta-analysis was to explore the current fMRI findings of hyperactivation or hypoactivation during emotion-regulation tasks, and to compare between BD patients and healthy control group in task performances of response time and accuracy. Therefore, providing a functional biomarker of converged brain regions related with emotional processing in BD using the Activation-likelihood (ALE) meta-analysis.

Even with the limitations of a small sample, that made impossible to apply a correction for p-value thresholds, and the fact that it consisted only of adult bipolar patients, the results suggest that the anterior cingulate cortex shows an important role in emotion regulation in BD, which presents a reduced activation in response to facial stimuli *(figure 8).* Our sub-group investigation revealed that bipolar patients displayed longer response time than HC, but HC showed higher accurate response rates. Consequently, our study represents a potential biomarker for the diagnosis and management of BD and explores reaction times and accurate response rates in BD patients. Additional studies are required to establish how these functional changes can be used to detect disease progression or utilized in therapeutic interventions.

Future recommendations

To better understand the pathophysiology of emotion dysfunction in BD and offer reliable diagnostic biomarkers for BD, future research should develop cross-sectional studies between bipolar stages and medicated or unmedicated patients,

to consent the viability of meta-analyses across different factors that may affect functional or structural modifications, also studying the impact of other behavioral domains in BD such as cognition or pain processing[4].

Neural correlates between emotional dysregulation implicated in BD and suicide

Preventing suicide in individuals with early-onset bipolar disorder (BD) is still challenging. Diffusion magnetic resonance imaging studies in BD have labeled neural correlates of emotional dysregulation implicated in BD and suicide. The use of diffusion magnetic resonance imaging was able to identify neural evidence of suicide attempts in adults with childhood-onset BD who have been clinically tracked for up to 19 years as part of the COBY (Course and Outcome of Bipolar Youth) study. Diffusion magnetic resonance imaging data were examined in 68 adults with BD: 20 in the suicide attempter (SA+) group and 48 in the non-suicide attempter (SA-) group.

Analyses showed a main effect of group on fractional anisotropy. Particularly, the SA+ group showed diminished fractional anisotropy than the SA- and healthy control groups in the middle portion of the forceps minor and in the anterior and posterior portion of the right cingulum bundle (CB). Irregularities in the FMIN, but not CB, were also associated with suicidal ideation and levels of emotional distress at scan. FMIN and CB abnormalities have been correlated with emotional dysregulation in BD. These findings suggest that the FMIN might represent a marker of suicidal ideation and, more generally, emotional distress, while CB may constitute a specific marker of attempted suicide[134].

Neural abnormalities in emotional response in pediatric bipolar patients

The presence of neural anomalies in emotional response in pediatric bipolar patients is clear, despite this, many aspects related to emotional dysregulation with neuroanatomical alterations are yet to be explored; In particular, recent studies over the past year have sought to clarify the possible link between ED and

different mood phases of pediatric bipolar disorder (PBD) or late positive potential (LPP) as a marker of emotion dysregulation. In the last year, two publications have worked to fill these questions.

The first one has set itself the objective of comparing the functional magnetic resonance imaging (fMRI) manifestations between different mood phases of pediatric bipolar disorder (PBD), exploring the variances in neural activities amongst manic, euthymic PBD and HCs during emotional response inhibition.

Coincidentally imaging of neural activity was recorded during an emotional Go/Nogo performance, and the effect of emotional response inhibition was analyzed. Neural activities were compared amongst the three categories.

The outcomes showed that in the presence of emotional versus neutral distractors, both manic and euthymic PBD subjects analogously showed prevalent increased activities in the cognitive and emotional regulation circuits in contrast with healthy individuals. Compared with euthymic PBD patients, those with manic PBD demonstrated improved activities in the left superior frontal gyrus. Hyperactivity in the left superior frontal, left middle frontal and right inferior frontal gyrus in manic PBD was positively associated with false response errors.

In conclusion is reasonable to support that increased activity in the left superior frontal gyrus might be distinctive of manic episodes in PBD patients, and such a discrepancy between manic and euthymic phrases may be the result of a greater emotional dysregulation. (Manic and euthymic states in pediatric bipolar disorder patients during an emotional Go/Nogo task: A functional magnetic resonance imaging study)[230].

The second study focused on the late positive potential (LPP), wondering if it could be a marker of emotion dysregulation in youth with pediatric bipolar disorder (PBD), while simultaneously trying to provide cortical and deep gray matter correlates of the LPP in youth, specifically, youth with PBD.

Twenty-four 7 to 17 years-old children with PBD and 28 healthy controls (HC) were tested for cortical thickness and deep gray matter volumes through magnetic

resonance imaging and LPP measurement provoked by passively viewing emotional faces through electroencephalography.

Discoveries supported that PBD had a more pronounced LPP amplitude for happy faces and a thinner cortex in prefrontal areas than HC. While contemplating both groups, a higher LPP amplitude was linked with a thicker cortex across occipital and frontal lobes, and with a reduced right globus pallidus volume. Furthermore, a higher LPP amplitude for happy faces was correlated with smaller left caudate and left globus pallidus volumes throughout both groups. Ultimately, the LPP amplitude correlated negatively with right precentral gyrus thickness across youth with PBD, but positively across HC.

With these assumptions it is possible to state that the Neural correlates of LPP in youth included fronto-occipital areas are related with emotional processing and control. The opposite correlation between BPD and HC of LPP amplitude and right precentral gyrus thickness might justify the inefficacy of the emotional control system in PBD.

As a last mention, the neuroanatomical correlates with impulsivity and aggression have already been displayed in the paragraph about risky behavior[209].

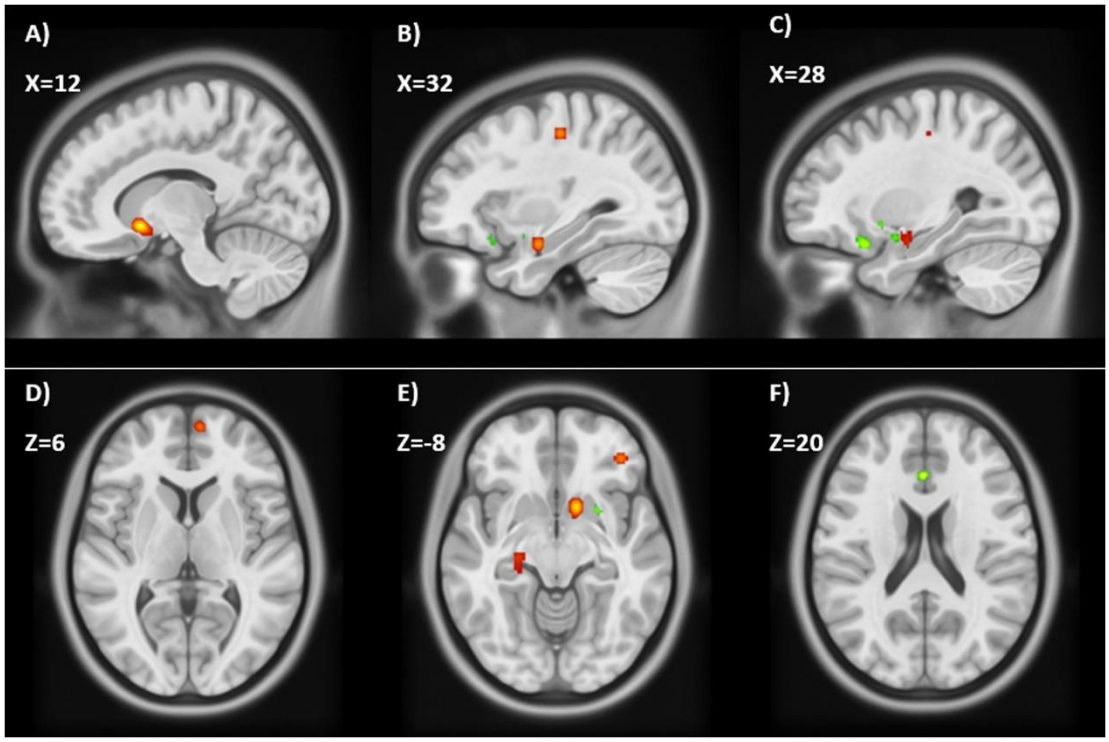

Figure 8 ALE maps of hyperactivation (red) and hypoactivation (green) in BD patients vs. HC. A) Caudate head, B) amygdala and precentral gyrus, C) inferior frontal gyrus, putamen and amygdala, D) medial frontal gyrus, E) caudate, sub-gyrus, putamen and amygdala, and F) anterior cingulate.

4. *Appetite hormone dysregulation, emotional dysregulation, and bipolar disorder*

Appetite hormone dysregulation and executive dysfunctionality in adolescents with bipolar disorder and disruptive mood dysregulation disorder

Appetite hormone dysregulation could have a role in the pathomechanisms of bipolar disorder and chronic irritability. Nevertheless, its link with executive dysfunction bipolar patients and those with disruptive mood dysregulation disorder (DMDD) remains uncertain.

A 2022 study included 20 adolescents with bipolar disorder, 20 adolescents with DMDD, and healthy controls[102]. Fasting serum levels of appetite hormones, including leptin, ghrelin, insulin, and adiponectin were measured. All participants finished the Wisconsin Card Sorting Test. Generalized linear models with adjustments for age, sex, body mass index, and clinical symptoms discovered that

subjects with DMDD had increased fasting log-transformed insulin levels compared to the control group.

Youngsters with DMDD executed worse in terms of the number of tries required to complete tasks in the first category ($p = 0.035$), similarly adolescents with bipolar disorder faced difficulties in terms of number of categories completed ($p = 0.035$). A positive correlation was detected between log-transformed insulin levels and the number of tries required for the first category ($\beta = 1.847$, $p = 0.032$). Adolescents with DMDD, but not those with bipolar disorder, were more prone to exhibit appetite hormone dysregulation in comparison to healthy controls. Augmented insulin levels were also associated to executive dysfunction in these patients. Future prospective studies must clarify the temporal association concerning appetite hormone dysregulation, executive dysfunction, and emotional dysregulation[99].

Appetite hormone dysregulation, body mass index, and emotional dysregulation in nonobese adolescents with first onset of bipolar disorder, major depressive disorder and schizophrenia: a cross-sectional association study

Coherently, with the aim of strengthening the evidence in favor of a role of appetite hormones in emotional dysregulation, another study has been published in the last year that aims to deepen this correlation by observing the association between emotional imbalance and appetite hormone in nonobese adolescents with first-episode schizophrenia, bipolar disorder, and major depressive disorder.

The study surveyed a sample of 22 adolescents with schizophrenia[101],with bipolar disorder, [131] with major depressive disorder and[189] healthy age-, sex-, and body mass index (BMI)/BMI percentile-matched controls. Emotional regulation symptoms were determined using the parent-reported Child Behavior Checklist—Dysregulation Profile.

As previously demonstrated by the first study, what has emerged is that minors with first-episode schizophrenia, bipolar disorder, and major depressive disorder presented greater emotional dysregulation symptoms than the control group. Adolescents with bipolar disorder exhibited higher log-transformed levels of insulin and reduced log-transformed levels of leptin compared with the control group. BMI and log-transformed ghrelin levels were positively correlated with emotional dysregulation symptoms.

Therefore, it is reasonable to assume that emotional dysregulation and appetite hormone disturbance could play a role in the early stage of severe mental disorders. Nevertheless, more studies are obliged to clarify the unidirectional or bidirectional association of emotional dysregulation with BMI/BMI percentile and appetite hormones between patients with severe mental disorder[98].

5. Inflammation and ED in BD

Numerous evidence chains the role of peripheral inflammatory markers and stress in the multifactorial etiology and physiopathology of BD, ADHD, and BPD. In fact, neural circuits that control emotions appear particularly vulnerable to inflammatory insults and peripheral inflammation, which can impact the neuroimmune environment of the central nervous system. To this date, few studies have inspected the link between ED and inflammation in BD, ADHD, and BPD. The evaluation has researched the known associations and mechanisms linking ED and inflammation in general, and clinically, in BD, ADHD, and BD.

In BD, some revisions verified that proinflammatory mediators are related with diminished brain volume in key areas responsible for ER. Studies found a positive correlation among inflammation and alterations of networks responsible of emotional processing and regulation. Furthermore, although a certain level of chronic inflammation is presents in most BD patients, certain subgroups seem more prone to peripheral (and possibly central) inflammation, particularly those

with a higher recurrence of manic episodes. While indirect, there are certain associations between symptoms or mediators of ED and inflammation. For instance, both aggression and hostility have been related to alterations of specific inflammatory markers. Independent from the directionality of these results, integrating clinical symptoms of ED with markers of inflammation, stress, and limbic connectivity could benefit the characterization of the physiopathology of BD, ADHD, and BPD. Calculating potential vulnerability markers for ED remains crucial to identifying at-risk populations, as for example, peripheral blood inflammatory markers and cortisol levels and ER questionnaires. A joint valuation of these measures could thus be integrated into screening procedures for patients with a history of ELS or a familiarity with ED. As reinforced by preliminary results[139, 152, 184], the use of adaptive ER strategies might positively impact peripheral inflammation and, perhaps, modulate the sensitivity to stress. Exposed subjects could be trained to develop effective ER strategies through psychosocial interventions, cognitive-behavioral therapy (CBT), or mindfulness[163] and mindfulness-based cognitive therapy, for instance. While there are no studies assessing the relation between mindfulness, ED, and inflammation to our awareness, previous work on healthy adults reported that mindfulness was associated with lower peripheral IL-6, and this connotation was partially clarified by modifications in brain FC involving dlPFC [2].

Consequently, further investigation is necessary in this area, especially in the context of ED. To complete, early interventions that mark inflammation and ED could decrease the detrimental effects of these features on health and stress and ideally prevent or at least modulate the vicious cycle. Additional description of the circuits linking ER strategies to inflammation might help identify context-appropriate strategies[180].

2.10 Therapeutic approaches in managing emotional dysregulation in bipolar patients

The manage of patients with BD typically consists in pharmacotherapy. Yet, despite advances in these pharmacotherapies, remission and recovery rates remain unsatisfactory. In some longitudinal studies, half of patients experienced relapses despite optimal pharmacotherapy[178]. The limits of pharmacotherapy alone led to a growing interest in the development and adaptation of BD–specific psychotherapies[174]. Various well-established psychotherapy protocols have been considered in BD, such as family focused therapy (FFT), cognitive behavior therapy (CBT)[107] and Compassion focused therapy (CFT)[79].

Having indeed been established that heightened amygdala activity through emotion regulation of negative affect forecasts amplified risk of episode relapse during a 16-month follow-up in subgroups of BD patients[113] and that hypo-activity in the dorsomedial prefrontal cortex during emotion down-regulation is a predictor factor for increased probability of subsequent episode relapse in patients with bipolar disorder during a 16-month follow-up time[113] training certain neural networks in emotional regulation[122] could constitute a possible treatment target in BD, which might prevent new mood episodes, expand psychosocial and occupational functioning, and potentially onset in high-risk relatives[114, 133, 371].

From a clinical perspective, ED could be targeted by prevention programs to reduce the psychopathological burden in individuals with an increased risk of BD (FDRs)[216]. From a research perspective, a better understanding of ED in BD could help future research into the biological, psychological, and environmental factors that influence this disorder, allowing taiolored ED psychological and pharmacological interventions[51].

DBT Therapy

The observational study found DBT to be both viable and suitable for the adolescent sample. The conclusions support the need for effectively powered RCTs to weigh the efficacy of DBT-based interventions in BD. In a recent network and component meta-analysis, manualized psychotherapies were related with less recurrence rates in BD outpatients when compared to control treatments[158]. Cognitive therapies, which involved two DBT studies, were allied with better stabilization of depressive symptoms than TAU. Outside establishing viability and suitability, the results were auspicious with some favorable post-intervention clinical outcomes in all available trials. Notwithstanding the limitations of the reviewed studies (the small sample dimension, a high level of heterogeneity in methods, outcome measures, and participant characteristics, and a substantial risk of bias), the overall suggestion advises potential benefits of DBT for common features of BD such as depressive symptoms, poor emotion regulation, suicidality, or executive dysfunction.

Published studies steadily support that DBT-based interventions are practicable and tolerable for patients with BD. These revisions also suggest this study may be effective for improving several core symptoms of BD. Upcoming large and well-designed RCTs are now desirable to establish the efficacy of DBT-based interventions for improving specific clinical outcomes in BD. In spite of this evidence, psychotherapeutic interventions remain second- and third line in several clinical guidelines for BD [107, 372].

Compassion focused therapy (CFT)

In addition, Compassion focused therapy (CFT) has also demonstrated to be performant in educating bipolar patients about emotional regulation and lessening elevated aspects of competitiveness and up rank status evaluation. The manic stage of disturb is frequently accompanied by a sense of superiority, elevated confidence, energized behavior, positive affect and social dominance. This is the first study to examine the feasibility of a 12 module CFT group, with the aim to help people with a diagnosis of bipolar disorder understand the effect of evolved competitive, status-regulating motivation on their mental states and the

value of cultivating caring and compassion motives and their psychophysiological regulators.

Qualitative statistics from three focus groups exposed that participants found CFT useful into giving them insight about: how evolution has increased to a number of difficulties for emotion regulation (called tricky brain) which is not one's fault; an evolutionary comprehension of the nature of bipolar disorders; growth of a compassionate mind and practices of compassion focused visualizations, styles of thinking and behaviors; tackling issues of self-criticism; and creating a compassionate self when coping with life difficulties. These promoted their emotional regulation and social relationships too[79].

Virtual reality as a sensitive behavioral measure and a method for training emotional regulatory abilities

Virtual reality has been suggested to be a potential tool for training psychological skills related to social anxiety through exposure therapy. However, to this date, documented efficacy of VR in treatment is limited [97]. Even though more studies are required in regard to the efficacy of VR in treatments, it is possible that the current VR paradigm could not only be a sensitive behavioral measure but also of significant in training emotional regulatory capabilities by offering exposure to life-like situations [114].

As introduced in the section about the link between alexithymia, ED e il risk of developing bipolar disorder *(2.6.7.),* increasing emotional awareness could have positive effects in emotional dysregulation, reducing its intensity and instability. The most appropriate therapy for this purpose, as announced by a recent article, seems to be the dialectical behavior treatment, which directly targets Clarity and Attention, may be useful in reducing emotion dysregulation in patients with bipolar illnesses[60, 80, 81, 224]. Thereby, subjects addressed as high risk based on psychometric risk assessments may find benefit from early intervention to a) tracking and attending feelings in reaction to an external or internal stimulus, and

b) correctly identify the source and form of emotions they feel could potentially reduce affect intensity and instability [214].

DBT-informed skill-building education course for families

Continuing the theme of possible therapies to improve the management of emotional dysregulation in bipolar disorder, it is important to underline that often this condition involves a daily and not indifferent emotional, psychic, and physical load, not only for the patients, but also for their families. There are a range of educational treatments for carers who have a family with a mental health issue. However, for people with one or more emotional dysregulation disorders, there are restricted alternatives. A novel article presents the findings of a pilot project using a quasi-experimental design with a survey of 270 to assess an intervention, Getting Off the Emotional Roller Coaster Skill-Building Family Education Course (GOER Family Course), for families facing and managing emotion regulation disorders in a loved one which are often misdiagnosed or co-occurring. This intervention was helpful in lowering caregiver strain while enhancing attitudes, knowledge, and abilities. It fills a critical vacuum in existing services for families confronted with obstacles and obligations that these conditions can provide, especially when wrongly diagnosed or getting inefficient treatment. While there is a need for additional study and adaption to virtual learning, the first results reveal beneficial impacts [147].

Emotional dysregulation is a multidimensional construct in which both bipolar and borderline patients differ from healthy controls and diagnosis is still complex.
Using the words of Ghaemi (2014) bipolar disease and borderline personality disorder are comparable in the nosological range of manifestations of mood lability and impulsivity, but vary considerably on all other diagnostic features, especially the presence of prior sexual abuse and a family history of bipolarism. They also diverge in clinical aspect of parasuicidal and self-harm tendencies.

Treatment response and neurobiological variations are also evident and consistent. [79]

This is why our study has used various scales to facilitate its diagnosis, focusing on the characteristics of emotionality, history of abuse, impulsiveness and decreased functionality.

CHAPTER 3. AIM OF THE STUDY

The current study aims to investigate and quantify differences between patients with BD, those with BPD, and healthy controls in (a) emotional dysregulation using Difficulties in emotion dysregulation scales (DERS), (b) impulsivity assessed by Barratt Inhibition Scale (BIS-11), (c) early childhood abuses using the Child Trauma Questionnaire (CTQ) and (d) daily functioning with the World Health Organization Disability Assessment Schedule (WHODAS.2).

This study aims to assist clinicians in the challenging task of distinguishing between patients with BD and BPD, thereby contributing to the refinement of the earlier diagnosis of these disorders.

CHAPTER 4. MATERIAL AND METHODS

The current case-control research was done in conformity with the recommendations of the Helsinki Declaration of 1975. All participants provided their informed consent to participate in the study after they had received a comprehensive description of the procedures.

4.1 SAMPLE

Patients with a diagnosis of BD and BPD according to the Diagnostic and Statistical Manual of Mental Disorders V Edition (DSM-V) were selected from the Psychiatric Ward at the Padua University Hospital, between July 2021 and December 2022.

The inclusion criteria for all subjects were:

- diagnosis of BD or BPD,
- age from 18 to 75 years,
- stable pharmacotherapy,
- stable clinical parameters.

Exclusion criteria were:

- traumatic head injury with unconsciousness,
- past or present major illness or neurological disorders,
- any (for HC) or additional psychiatric disease or mental impairment,
- dementia or cognitive deterioration according to DSM V criteria, and Mini Mental State Examination (MMSE) score <25. [78]

Preliminary BD and BPD diagnoses of potential participants were determined according to DSM V criteria by their respective psychiatrists, who gave the investigators all relevant clinical information on the potential participants'

previous and present health records. All clinical diagnoses were confirmed by evaluators with considerable training through the Structured Clinical Interview for DSM-V-Patient Edition (SCID-I and SCID-II) (SCID-I and SCID-II). [74]

In all, 74 individuals and 62 HCs respected the inclusion/exclusion criteria. The patient group was composed by 42 people diagnosed with BP and by 32 persons diagnosed with BPD. They were meticulously matched by age, gender, and educational level.

All HC were examined for a present or lifetime history of any Axis I and II disorders using the SCID- I and SCID-II.[74]

Participants with DSM V Axis I or II illnesses and/or family record of mood disorders or schizophrenia were excluded from the HC group. All other qualifying criteria were the same as those for the patients group.

All patients were medically stabilized, euthymic, recruited right before the hospital discharge and they were under stable pharmaceutical.

4.2 CLINICAL ASSESMENT

The Barratt Inhibition Scale (BIS-11) [6] for trait impulsiveness, the Child Trauma Questionnaire (CTQ) [26] for childhood abuse and maltreatment and the Difficulties in Emotion Regulation Scale (DERS) were used to highlight the characteristics associated with the emotional dysregulation in patients with BD and BPD. Moreover, the daily functioning and disability was assessed by the 36-items World Health Organization Disability Assessment Schedule (WHO-DAS 2.0).

All data about age of onset and the duration of illness, past psychiatric history including number of previous depressives, manic, or hypomanic episodes, the presence psychotic symptoms were also investigated. Moreover BMI, psychiatric

and medical comorbidity, substance use, hospitalization and suicidal attempts, psychiatric familiarity, and current pharmacological treatment were collected.

4.3 EMOTION REGULATION ASSESMENT

To this day, a univocal and collective definition of ED has not yet been given [47] and an inclusive view on this matter is challenging [195]. Various approaches were advanced providing a focus on specific aspects of ED.

Various questionnaires are used in the evaluation of emotional dysregulation in psychiatric patients, first of all the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004) aims to evaluate the struggle in regulating negative emotions.

The Difficulties in Emotion Regulation Scale (DERS) is a 36-item test measuring six techniques to manage emotion: (1) non-acceptance of emotional response (DERS-NonAccept) (e.g. 'If I'm upset, I feel guilty for feeling that way'), (2) difficulty in applying goal-directed behaviors (DERS-Goals) (e.g. 'If I'm upset, I have trouble focusing'), (3) struggles in managing impulsive behaviors (DERS-Impulse) (e.g. 'If I'm upset, I become incontrollable'), (4) limited access to emotion regulation strategies (DERS-Strategy) (e.g. 'If I'm upset, it takes me a long time to feel good again'), (5) lack of emotional recognition or clearness (DERS-Clarity) (e.g. 'I am confused on how I feel'), and (6) lack of emotional consciousness (DERS-Aware) (e.g. 'I pay attention to how I feel'). [72]

Other tests that do not directly diagnose emotional dysregulation, but are often able to detect features associated with it and present the patients analyzed, are the Barratt Impulsiveness Scale-11 (BIS-11) for impulsivity, the Childhood Trauma Questionnaire (CTQ) that inspects for a history of abuse and neglect in children over the age of 12 and the World Health Organization Disability Assessment

Schedule (WHODAS 2.0), able to measure health and disability among the population or in clinical practice.

The Childhood Trauma Questionnaire (CTQ) is a 28-item, self-report that inspects for a history of abuse and neglect in children over the age of 12[28]. This test was created as a screening tool for records of abuse and neglect. The self-report comprises a 28-item test that examines 5 categories of maltreatment — emotional, physical, and sexual abuse, and emotional and physical neglect. CTQ questionnaires are often used to establish treatment programs, performing child custody investigations, and screening specific populations. An overall of 5 minutes is necessary to complete the exam. A 5-point Likert scale is used for the replies which range from “Never True” to “Very Often True” [391].

The BIS-11 (Patton, Stanford, & Barratt, 1995; Stanford et al., 2009) is a 30-item self-report test of impulsive personality characteristics. For this questionnaire, the occurrence of common impulsive (ie, “I do things without thinking”) or non-impulsive (“I am self-controlled”) behavioral traits are scored on a scale from 1 "Rarely/Never" to 4 "Almost Always/Always". Answers across all items are totaled to an overall score of 30 to 120 points, having higher values reflecting more impulsiveness. Scores on the BIS-11offer high test-retest reliability and internal consistency [158].

The World Health Organization Disability Assessment Schedule (WHODAS 2.0) is a useful, flexible evaluation tool able to measure health and disability among the population or in clinical practice.

This questionnaire measures the degree of functioning in six domains of life:

1. Cognition – understanding and communicating.

2. Mobility - movement and ability to travel.

3. Self-care – performing selfcare hygiene's practices, like dressing, eating and staying alone.

4. Getting along - interacting with other people.

5. Life activities – domestic and professional/academic obligations.

6. Participation - engaging in communal activities, participating in society.

WHODAS 2.0 offers a standard measurement of the impact of any health condition in terms of functionality. Being a global indicator, the instrument does not target a specific condition - it may therefore be used to compare impairment caused by different disorders. WHODAS 2.0 also makes it feasible to create and assess the impact of health and health-related activities. The measure has shown beneficial for measuring health and disability levels in the general population and in specialized groups (ie persons with a range of various mental and physical problems) (ie people with different mental and physical conditions). Additionally, WHODAS 2.0 makes it simpler to create health and health related treatments, and to assess their impact [248].

4.5 DATA ANALYSIS

Demographic and clinical characteristics

Sociodemographic and clinical characteristics of the selected groups of patients (i.e., BD, BPD, and HC) were compared using chi ‐ square tests for categorical variables (i.e., gender, current mood state and past and current pharmacotherapy) and one ‐ way evaluations of difference (ANOVA) for continuous variables (i.e., age, years of education, duration of illness, number of episodes, YMRS and BDI scores), associated with Tukey post hoc comparisons in case of statistical significance. The threshold of significance was set at $p<0.05$ for all tests.

Clinical test performance

The results of the psychometric measures (CTQ, DERS, BIS-11, WHODAS 2.0) of the three mentioned groups were compared using an analysis of variance (ANOVA) supplemented by Tukey's post hoc analysis. The threshold of significance was set at $p<0.05$ for all tests.

Data analysis was conducted with Jamovi (Version 1.2) [Computer Software], get by https://www.jamovi.org e R (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/).

CHAPTER 5. RESULTS

Forty-two patients with BD, 32 subjects diagnosed with BPD, and 62 healthy controls (HC) were recruited.

The analysis of demographic and clinical characteristics of participant were enlisted in *Table 1 and 2.*

The rating's analysis identified most of the values of the scales considered as significant.

There was a significant difference between patients with BD, BPD, and healthy controls in the BIS-11 ($p= 0.010$), in the CTQ ($p<0.001$), in the WHODAS.2 ($p<0.001$) and in the DERS ($p<0.001$) scores.

Detailed clinical data are presented in *Table 3.*

In the DERS, the ANOVA analysis of patients revealed a significant difference between the three groups ($p<0.001$).

Specifically, for "DERS TOTAL score", post hoc analysis confirmed a significant difference between all the three groups: between BPDs and controls ($p<0.001$), between BDs and controls ($p=0.005$), and between BD and BPD patients ($p<0.001$). Values were significantly higher for patients with BPD, both in DERS TOTAL score and in all its subcategories, except for "DERS awareness" and "DERS difficulties engaging in goal-directed behavior".

For "DERS non-acceptance", post hoc analysis revealed a significant difference between between patients with BD and controls ($p=0.04$), patients with BPD and

HCs ($p<0.001$) and between BD and BPD patients ($p=0.05$), with higher values for patients with BPD.

For “DERS difficulties engaging in goal-directed behavior”, post hoc analysis revealed a significant difference between BPD and controls ($p<0.001$), but no significant difference between BD and controls ($p=0.07$), and between patients ($p=0.06$) was found. The highest values pointed in the direction of patients with BPD.

For “DERS strategies”, post hoc analysis revealed a significant difference among all the three groups: between patients with BD and BPD ($p<0.01$), and between BDs and controls ($p=0.015$) and between BPDs and controls ($p<0.01$), with higher values for patients with BPD.

For “DERS impulse”, post hoc analysis revealed a significant difference between patients with BD and controls ($p<0.001$), between patients with BD and BPD ($p=0.04$) and between BPDs and controls ($p<0.001$) with higher values for patients with BPD.

For “DERS clarity”, post hoc analysis revealed a significant difference between BPDs and controls ($p<0.001$), and between BD and BPD patients ($p=0.002$), but no significant difference between among patients with BD and HCs ($p=0.08$), was found. The highest values pointed in the direction of BPD patients.

For “DERS awareness” no significant difference was observed between the three groups ($p=0.09$).

In the BIS-11 test the ANOVA analysis revealed a significant difference between the three groups ($p<0.005$). Specifically, for “BIS-11 TOTAL score”, post hoc analysis revealed a significant difference between BPDs and controls ($p=0.003$) and between patients with BD and BPD ($p=0.02$), but no significant difference between BDs and Hcs ($p=0.9$) was found.

For “BIS-11 attentive impulsivity”, post hoc analysis revealed a significant difference between patients with BPD and controls ($p<0.001$), between BDPs and

BDs (p=0.04), but no significant difference between patients with BDs and controls (p=0.1), with higher values for BDP patients.

For “BIS-11 motor impulsivity”, post hoc analysis revealed a significant difference between patients with BPDs and controls (p=0.03), but no significant difference between BDs and controls (p=0.6) and between BDPs and BDs (p=0.2), with higher values for patients with BPD.

For “BIS-11 non-planned impulsivity”, post hoc analysis revealed a significant difference between BPDs and controls (p=0.04), but no significant difference between patients with BD and Hcs (p=0.4) and between BPDs and BDs (p=0.2), with higher values for patients with BPD.

In the CTQ the BD the ANOVA analysis revealed a significant difference between the three groups (p<0.001).

Specifically, for “CTQ TOTAL score”, post hoc analysis revealed a significant difference between BPDs and controls (p<0.001), and between BDs and controls (p<0.001), but no significant difference between the two groups of patients (p=1) emerged. The values were higher and similar between the two categories of patients than the controls.

This kind of association was confirmed also by Tukey’s post hoc analysis in the CTQ subscales.

Specifically, for “CTQ emotional abuse”, post hoc analysis revealed a significant difference between BPDs and Hcs (p<0.001), and between BDs and Hcs (p<0.001), but no significant difference between patients with BD and BPD (p=1) was found, with higher values among patients.

For “CTQ physical abuse”, post hoc analysis revealed a significant difference between BPDs and controls (p<0.001), and between BDs and controls (p=0.002), but no significant difference between patients with BD and BPD (p=0.6) emerged with higher values among patients.

For “CTQ sexual abuse”, post hoc analysis showed a significant difference between BPDs and controls ($p<0.002$) and between BDs and controls ($p=0.03$), but no significant difference between patients with BD and BPD ($p=0.6$) emerged with higher values among patients.

For “CTQ emotional neglect”, post hoc analysis revealed a significant difference between BPDs and controls ($p<0.001$), and between BDs and controls ($p=0.001$), but no significant difference between patients ($p=0.8$) was identified, with higher values among patients.

For “CTQ physical neglect”, post hoc analysis showed a significant difference between BPDs and controls ($p<0.001$), and between BDs and controls ($p<0.001$), but no significant difference between patients with BD and BPD ($p=1$) was found, with higher values among patients.

No significant difference was found between the three groups in the subcategory “CTQ Minimization Scale”.

In the WHODAS.2 test the ANOVA analysis revealed a significant difference between the three groups ($p<0.001$) with higher values for patients with BPD in both WHODAS TOTAL and all subcategories.

For “WHODAS.2 TOTAL score”, post hoc analysis revealed a significant difference between BPDs and controls ($p<0.001$), BDs and controls ($p<0.001$), and patients with BD and BPD ($p=0.004$).

Specifically, for “WHODAS.2 cognition”, post hoc analysis revealed a significant difference between BPDs and controls ($p<0.001$), between BDs and BPDs ($p=0.02$) and between BDs and controls ($p=0.02$), with higher values for patients with BPD.

For “WHODAS mobility”, post hoc analysis showed a significant difference between BPDs and controls ($p<0.001$), between BDs and controls ($p=0.008$) and among patients with BD and BPD ($p=0.02$), with higher values for BPD patients.

For “WHODAS self-care”, post hoc analysis revealed a significant difference between all the three groups: between BPDs and controls ($p<0.001$), between

patients with BD and BPD (p=0.001), and between BDs and controls (p<0.001), with higher values for borderline patients.

For “WHODAS.2 getting along”, post hoc analysis revealed a significant difference between BPDs and controls (p<0.001), between BDs and controls (p=0.03), and between patients with BD and BPD (p=0.003), with higher values for borderline patients.

For “WHODAS life activities”, post hoc analysis revealed a significant difference between BPDs and controls (p<0.001), and between BDs and controls (p=0.02), but no significant difference between patients with BD and BPD (p=0.12) was identified. The values were very similar and higher among patients than controls.

For “WHODAS participation”, post hoc analysis revealed a significant difference between BPDs and controls (p<0.001), and between BDs and controls (p<0.001), but no significant difference between patients with BD and BPD (p=0.08) was found, with higher scores for patients.

Table 1 Sociodemographic and clinical characteristics of the sample. NS=Non Significant.

	Level	**BD Spectrum**	**Borderline personality disorder**	**HC**	**p test**
Number		42	32	62	
Gender (%)	F	22 (52.4)	22 (68.8)	37 (59.7)	NS
	M	20 (47.6)	10 (31.2)	25 (40.3)	
Age (median [IQR])		44.50 [31.25, 54.75]	25.00 [20.00, 40.25]	31.00 [25.00, 48.75]	<0.001

Marital status (%)	Single	24 (58.5)	20 (62.5)	34 (54.8)	NS
	Married	10 (24.4)	7 (21.9)	26 (41.9)	
	Separated	6 (14.6)	5 (15.6)	2 (3.2)	
	Widower	1 (2.4)	0 (0.0)	0 (0.0)	
Years of scholarship (median [IQR])		13.00 [12.00, 16.00]	13.00 [11.75, 16.00]	17.00 [13.00, 19.00]	<0.001
Standardize by degrees of kinship (0= no, 1 child or parents, 2 brother or grandfather, 3 everything else) (%)	0	23 (56.1)	18 (56.2)	56 (90.3)	<0.001
	1	10 (24.4)	13 (40.6)	0 (0.0)	
	2	6 (14.6)	0 (0.0)	3 (4.8)	
	3	2 (4.9)	1 (3.1)	3 (4.8)	
Medical comorbidity_CAT (0=no, 1= yes) (%)	0	20 (47.6)	15 (46.9)	3 (4.8)	<0.001
	1	22 (52.4)	17 (53.1)	59 (95.2)	
Medical therapy_CAT (0=yes, 1=no) (%)	0	7 (17.1)	11 (34.4)	7 (11.3)	NS
	1	34 (82.9)	21 (65.6)	55 (88.7)	

Table 2 Comparison of patient sample characteristics (BD and BDP). NS=Non Significant.

	Level	BD Spectrum	Borderline personality disorder	p test
Number		42	32	
Gender (%)	F	22 (52.4)	22 (68.8)	NS
	M	20 (47.6)	10 (31.2)	
Age (median [IQR])		44.50 [31.25, 54.75]	25.00 [20.00, 40.25]	<0.001
Marital status (%)	Single	24 (58.5)	20 (62.5)	NS
	Married	10 (24.4)	7 (21.9)	
	Separated	6 (14.6)	5 (15.6)	
	Widower	1 (2.4)	0 (0.0)	
Years of scholarship (median [IQR])		13.00 [12.00, 16.00]	13.00 [11.75, 16.00]	NS
Standardize by degrees of kinship (0= no, 1 child or parents, 2 brother or grandfather, 3 everything else) (%)	0	23 (56.1)	18 (56.2)	NS
	1	10 (24.4)	13 (40.6)	
	2	6 (14.6)	0 (0.0)	
	3	2 (4.9)	1 (3.1)	
Duration of illness (years) (median [IQR])		17.00 [7.00, 27.00]	5.00 [2.00, 12.75]	NS
Current suicidal ideation (%)	No	36 (87.8)	23 (71.9)	NS
	Yes	5 (12.2)	9 (28.1)	
Age of onset (median [IQR])		24.00 [20.00, 30.00]	17.50 [14.75, 21.25]	<0.001

N° TS (median [IQR])		0.00 [0.00, 1.00]	2.00 [0.00, 3.00]	<0.001
Psychiatric comorbidity (0=yes, 1=no) (%)	0	18 (43.9)	19 (59.4)	NS
	1	23 (56.1)	13 (40.6)	
Medical comorbidity_CAT (0=no, 1= yes) (%)	0	20 (47.6)	15 (46.9)	NS
	1	22 (52.4)	17 (53.1)	
Current substance use (%)	No	30 (73.2)	16 (51.6)	NS
	Yes	11 (26.8)	15 (48.4)	
TP antidepressant_CAT (0=yes, 1=no) (%)	0	9 (22.0)	22 (68.8)	<0.001
	1	32 (78.0)	10 (31.2)	
TP stabilizing_CAT (0=yes, 1=no) (%)	0	31 (73.8)	15 (46.9)	NS
	1	11 (26.2)	17 (53.1)	
TP antipsychotic_CAT (0=yes;1=no) (%)	0	40 (95.2)	29 (90.6)	NS
	1	2 (4.8)	3 (9.4)	
Medical therapy_CAT (0=yes, 1=no) (%)	0	7 (17.1)	11 (34.4)	NS

Table 3 Clinical test performance of patients and controls about emotional dysregulation. Lines with a lighter color represent the subscales with not significant results.

	BD Spectrum	Borderline personality disorder	HC	p test
CTQ emotional abuse (mean (SD))	10.38 (4.74)	10.44 (6.34)	6.56 (2.32)	<0.001
CTQ emotional neglect (mean (SD))	10.94 (4.17)	11.56 (6.20)	7.79 (3.15)	<0.001
CTQ physical abuse (mean (SD))	7.70 (3.30)	8.45 (5.28)	5.47 (1.04)	<0.001
CTQ physical neglect (mean (SD))	7.45 (2.00)	7.42 (3.04)	5.73 (1.36)	<0.001
CTQ scale minimization (mean (SD))	0.62 (0.78)	0.63 (0.96)	0.65 (0.85)	1
CTQ sexual abuse (mean (SD))	7.10 (4.11)	7.97 (5.81)	5.19 (1.07)	<0.001
CTQ TOT (mean (SD))	46.36 (13.26)	46.45 (21.31)	31.23 (5.44)	<0.001
DERS difficulty in goal-directed behavior (mean (SD))	14.32 (4.49)	16.88 (5.25)	12.21 (4.42)	<0.001
DERS clarity (mean (SD))	11.60 (4.62)	15.19 (5.34)	9.68 (3.66)	<0.001
DERS lack of acceptance (mean (SD))	14.53 (6.72)	17.88 (6.96)	11.55 (4.93)	<0.001
DERS impulse control difficulties (mean (SD))	14.88 (5.67)	17.75 (6.14)	9.60 (3.72)	<0.001
DERS emotional regulation strategies (mean (SD))	18.52 (5.77)	25.56 (8.39)	14.92 (5.23)	<0.001
DERS reduced self-awareness (mean (SD))	5.95 (2.68)	7.44 (3.40)	6.08 (3.03)	0.07
DERS TOT (mean (SD))	86.88 (21.42)	108.61 (28.30)	72.76 (18.49)	<0.001
BIS-11 attentional impulsiveness (mean (SD))	16.28 (3.96)	18.27 (3.56)	14.87 (2.89)	<0.001
BIS-11 motor impulsivity (mean (SD))	21.44 (5.56)	23.34 (5.07)	20.58 (4.14)	<0.05

BIS-11 non-planned impulsivity (mean (SD))	25.05 (5.67)	28.50 (6.03)	26.42 (5.86)	<0.05
BIS-11 TOT (mean (SD))	62.77 (11.61)	70.11 (12.78)	61.71 (10.70)	<0.005
WHODAS activities daily life (mean (SD))	2.15 (1.18)	2.64 (1.21)	1.58 (0.65)	<0.001
WHODAS understand and communicate (mean (SD))	2.04 (0.91)	2.56 (0.90)	1.60 (0.57)	<0.001
WHODAS self-care (mean (SD))	1.65 (0.72)	2.20 (0.93)	1.13 (0.27)	<0.001
WHODAS mobility (mean (SD))	1.69 (0.92)	2.23 (1.09)	1.18 (0.50)	<0.001
WHODAS participation in social life (mean (SD))	2.54 (0.82)	2.92 (0.82)	1.71 (0.56)	<0.001
WHODAS getting along (mean (SD))	2.02 (0.76)	2.66 (1.06)	1.59 (0.61)	<0.001
WHODAS TOT (mean (SD))	12.34 (4.02)	15.27 (5.15)	8.81 (2.32)	<0.001

CHAPTER. 6 DISCUSSION

Compared to HC, patients with BD showed significantly higher values in DERS, CTQ and WHODAS.2 total scores, while they did not differ significantly from HCs in BIS-11 total scores.

Patients with BD presented significant lower scores compared to those with BPD in DERS, BIS-11 and WHODAS.2 total scores, while the difference was not significant in CTQ total score.

On the other side, patients with BPD exhibited significantly higher DERS, BIS-11, CTQ and WHODAS.2 total scores compared to HCs.

Patients with BD displayed significant higher values in DERS subscales compared to HCs, except for “DERS difficulties engaging in goal-directed behavior”, “awareness” and “clarity” subscales.

Also, patients with BD had lower ratings than those with BPD in DERS subscales, except for “DERS difficulties engaging in goal-directed behavior” and “awareness” that did not show significant differences between patients’ subgroups.

Patients with BPD had significant higher values in DERS subcategories compared to HCs, except for “DERS awareness”, where the difference was not significant.

In the BIS-11 score, patients with BD did not differ significantly from controls in any subcategory, while they exhibited significantly lower values in all subdomains of BIS-11, except for "BIS-11 motor impulsivity" and "BIS-11 not planned impulsivity" compared with BPD patients.

Patients with BD displayed significantly higher rating in all CTQ subscales compared to HCs, with the exception of “CTQ scale minimization” where the difference was not significant.

Comparing patients with BD and those with BPD, no significant differences were found in any subcategories between the two groups.

Conversely, patients with BPD showed significantly higher scores in all CTQ subscales compared to HCs, with the exception of “CTQ scale minimization” where the difference was not significant.

Finally, patients with BD presented significant higher scores compared to HCs in all subscales of WHODAS.2.

Comparing patients with BD and those with BPD the difference was significant in all subcategories except for "WHODAS.2 life activities” and “WHODAS.2 participation”.

Also, patients with BPD presented significant higher values in all subscales compared to HCs.

Comparing the results obtained in the scale DERS with the prior literature, this current study is consistent with the recognized role of emotional dysregulation in models of BD[92] [191] and BPD[126] [218] pathophysiology, providing evidence that patients with BD and BPD have higher scores of emotional dysregulations compared to HCs.

These outcomes are compatible with the thorough meta-analysis published by De Prisco [51] and with the recent study authored by A. Miola[162], in which it was noted that BD subjects had higher values in “DERS TOTAL score” than controls. Instead, different results occurred in the comparison between patients with BD and BPD. In fact, A. Miola previous study found no discrepancies in “DERS TOTAL scores” between subjects with BD and those affected by BPD, while in the present

research “DERS TOTAL score” values of BPD patients were significantly higher than those achieved by BD patients and controls.

Deepening the topic and observing the subcategories of the DERS scale, also in this case emerge results in accordance with the previous literature. Both A. Miola and De Prisco had observed higher scores in the DERS subdomains by patients with BD compared to healthy controls. Also, the first study had assessed higher scores for patients with BPD compared to those with BD in all DERS categories. In disagreement with the results of Miola the current analysis did not find a significant difference in the subdomain "Goal" and “awareness” between BDs and BPDs. In fact, if in the 2022 study patients with BPD had significantly higher values than BDs, in our study a significant difference between the two groups in these subcategories was not identified.

In support of the results, further literature has revealed the presence of a reduced impulse control in emotional dysregulation in BPD compared to BD, impaired emotion regulation strategies, as well as heightened impulsivity reported in BPD. These aspects might explicate many of the behavioral difficulties typical in this disease, including high mood unpredictability and willful self-harm [118]. Actually, individuals affected by BPD demonstrated a two-fold greater relative risk of parasuicidal self-harm compared to BD [375].

These results are in line with further studies that shown how in patients with BD scores of DERS were higher than controls. One of this analysis also observed that these scores were positively correlated with higher scores of Barratt Impulsivity Scale (BIS-11), Suicidal ideation, Suicide behavior scores, Suicide Probability Scale (SPS), and Buss-Perry Aggression Questionnaire (BPAQ), suggesting that greater emotional dysregulation may be a risk factor for impulsivity and suicidality.

Continuing the subject about the scale BIS-11, our analyses have observed that patients with BDP presented significantly higher values compared to BD patients and controls. Even in the subcategories the same trend manifested, with the only exception that there was not a significant difference among patients in “motor impulsivity” and “non-planned impulsivity”.

As far as BD patients are concerned, the absence of significant differences from controls, nor from patients with BPD in “motor impulsivity” and “non planned impulsivity”, disagrees with the studies of Kulacaoglu and Izci (2022) and Buyuksandalyaci Tunc and Gul (2023). These analyses aimed to observe the levels of impulsivity among bipolar patients through the BIS-11 scale, revealing that the “motor” and “total scores” of the Barratt Impulsivity Scale (BIS-11) were greater in bipolars than in patients with schizophrenia and healthy controls.

According to the aforementioned study, in patients with BD scores of DERS and Barratt Impulsivity Scale (BIS-11), were highly related. In fact, a substantial positive link was discovered between all subscales of DERS and attention and motor subscales of BIS-11 [38].

These new results will certainly have to be deepened, as the presence of impulsive behavior is of great importance,being high values of BIS-11 “non-planning impulsiveness” revealed to be a predictor of suicidal ideation in BD[120]. Accordingly, “DERS TOTAL” and “BIS TOTAL” scores of patients with BD with suicide attempts were considerably higher than bipolar subjects with suicidal thoughts and bipolar patients with neither attempt nor planning [34]. This relationship, according to the regression analysis, indicated that “strategies”, “clarity”, and “non-planning impulsiveness” are predictors of suicidal planning in bipolar patients. These results suggested that suicide conduct has a substantial association between emotional dysregulation and impulsivity in BDs, and that suicidality may arise in people with this disorder who have trouble in emotion regulation [34]. Clinicians must critically analyze emotional dysregulation and impulsivity within this population to elucidate the role of impulsivity among patients with BD and create therapeutic options in suicide prevention [106].

Third, CTQ, compared to HCs, patients with BD and BPD displayed similar and significantly higher “CTQ total scores” compared to HCs.

It is not unexpected that BPD patients provided history of childhood abuse, given it is believed to be the most well validated psychosocial risk factor for BPD. [72] [111] On the other side, the high CTQ score in the BD group is less expected. Recent

research indicated that especially people diagnosed with BD demonstrated significant rates of childhood trauma, when compared to general population [231] [105]. For example, a 2021 study intended to investigate if childhood maltreatment and emotion dysregulation affected automatic thoughts (ATs) and meta-cognitions (MCs) in BD. ATs were determined by CTQ “physical abuse”, “impulse” and “non-accept” subscales of DERS. Results showed increased values in patients with BD of both scales, implying that emotion dysregulation and childhood traumas are related with cognitive processes such as MCs and ATs in BD. The analysis remarked how the cognitive processes can generate numerous clinical symptoms and how emotion dysregulation and childhood traumas could be viewed as psychopathological components that might alter the development of mood disorders via multiple components. Future investigation with bigger samples is needed to better comprehend the impacts of these components [377].

As additional support of this hypothesis, a meta-analysis demonstrated a considerable relationship between childhood trauma and later mental diseases. [158] A prior systematic study revealed that childhood maltreatment predicted deteriorating clinical course in BD given its substantial relationship with early start of disease, suicidality, and drug abuse problem in persons with BD.

Abundant evidence supports child maltreatment as a risk factor for developing bipolar illness [29]. The most relevant connections with BD are cases of past physical, sexual, and emotional abuse, as well as physical and emotional neglect [292]; The greatest of these is for emotional abuse, which is detected four times more frequently in patients with BD than healthy individuals [292]. Moreover, BD patients have a larger prevalence of early adversity.

This association has also been underlined by recent researches, such as the one focused on relations of childhood emotional abuse and alexithymia to the clinical course of BD, indicating how the struggles in regulating emotions may clarify these correlations, being a mediator factor between childhood emotional abuse and alexithymia on depressive and manic episodes as well as suicidal thoughts in female patients with BD.

The study confirmed that childhood emotional maltreatment and difficulties in recognizing feelings were indirectly connected with depressed and manic symptoms as well as suicide thoughts. For this reason, individuals with BD who suffered emotional abuse throughout childhood, as well as struggling to recognize feelings reported more emotional dysregulation. These individuals seemed to be more vulnerable to suffer of severe depressive and manic symptoms as well as suicidal ideation [114].

The possible biological reason behind this association has been suggested by the presence of alterations at the hypothalamic-pituitary-adrenal[290] axis, increased levels of BDNF and cytokines pro-inflammatory[291] and reduced volume of gray matter at the level of the limbic [292] system observed in patients with history of childhood abuse, constituting a possible neurobiological substrate through which childhood trauma can be related to BD.

Fourth, in this investigation we confirmed that individuals affected by BD or by BPD displayed a greater functional impairment compared to HCs, as determined by WHODAS.2. Patients with BPD, in particular, had a greater degree of general dysfunction in daily activities, specifically in tasks involving cognition, mobility and relationship.

The current study has various limitations that should be noted when evaluating the findings. Initially, even though the population was defined in depth, the relatively small simple size restricted the generalizability of our results. Second, cross-sectional study design can limit our capacity to form assumptions about the causation of the data. Third, both type 1 and 2 bipolar disorder individuals were included in the bipolar sample, although the limited fraction of BD-2 patients did not allow us to separate studies comparing BD-1 and BD-2 sub-samples to the BPD

patients. Fourth, patients with BD and BPD were under pharmaceutical treatment that potentially constitute a bias, even though the pharmacological therapy facilitated the clinical stability. Fifth, we sought to alleviate the limit of the self-reported measurements, due to the integration. Sixth, patients were matched by sex, but not by age.

CONCLUSION

In conclusion, the study established a quantitative assessment of emotion dysregulation methods in BD and BPD, suggesting that both patients with BD and BPD display difficulties in emotion regulation compared to controls.

These results also propose that, compared to BPDs, individuals with BD display better emotion regulation strategies and less frequently resort to attitudes of non-acceptance, in addition to possessing an increased emotional clarity. Furthermore, patients with BD displayed less difficulties managing impulsive behaviors compared to those with BPD.

Another interesting aspect that emerged from our study is the propensity to impulsiveness. Patients with BD did not show increased impulsivity compared to healthy controls. In addition, BDs recurred to less impulsive behavior than those with BPDs, with two exceptions. In fact, both BD and BPD patients seemed to resort to the same level of unplanned impulsivity and motor impulsiveness.

The presence of childhood abuse, on the other side, was high in both groups of patients compared to controls but did not differ significantly from each other's. The only attitude used equally, both in patients and healthy controls, was the propensity to minimize or deny their traumatic experiences.

Finally, the level of dysfunctionality in daily activities appeared to be different between all groups, either comparing patients with BD to HCs, BDs to BPDs or patients with BPD to HCs.

From these assumptions, it could be useful to utilize the unique propensity of each disorder in achieving certain scores to facilitate differential diagnosis, through the administration of specific tests depending on the pathology considered, as well as make the diagnosis more precise.

Specifically, in case of diagnosed or suspected BD patients, it may be particularly useful to administer the DERS and the WHODAS.2 score, focusing in the “cognition”, “mobility” and “self-care” the subscales of the latter and in the "non-acceptance", "strategies" and "impulse" of DERS.

Considering patients with BPD, it may be useful to include in the diagnostic process the administration of the DERS, BIS-11 and WHODAS.2 scales, as these patients obtained distinctive results in such questionnaires. Deepening the matter, it may be useful to pay particular attention to the results obtained in the DERS subscales "non acceptance" "strategies" "impulse" and "clarity", BIS-11 "attentional impulsivity" and WHODAS.2 in all its categories, as they are particularly distinctive from both HCs and patients with BD.

To conclude, future bigger research with a prospective longitudinal design is necessary to confirm and to better understand such associations.

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