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Abstract

Background: Bipolar disorder (BD) is a severe and highly heterogeneous mental illness characterized by recurrent fluctuations in mood, energy levels, and behaviour. Debates persist regarding the optimal approach to manage the heterogeneity behind the broad concept of BD. In addition, precise neurobiological mechanisms differentiating the main BD subtypes, BD type I (BD-I) and BD type II (BD-II), remain a subject of ongoing research. In this context, exploration of structural brain networks can offer a relatively comprehensive representation of the complex organization of the brain, and can be coupled with an in-depth examination of the interplay among network covariance patterns, clinical and psychological functioning, and ratings of affective temperaments. However, such analyses have not been systematically investigated to compare BD subtypes. Indeed, affective temperaments appear to represent vulnerability factors or precursors of BD, and may constitute illness course-modifiers affecting the long-term prognosis of BD. Moreover, impairments in affective cognition increasingly are recognized as a core feature of BD. Notably, altered emotional processing, particularly facial emotion recognition (FER), is proposed as a candidate endophenotype of BD. Conducting such in-depth analyses may shed light on the pathophysiology underlying the main BD subtypes, may help mitigate the delay associated with achieving an accurate diagnosis of BD, and may inform a more accurate prognosis prediction and better-tailored interventions.

Methods: Thirty adult patients with BD-I, 30 with BD-II, and 45 age- and sex-matched healthy controls (HC) underwent a structural MRI scan as well as a battery of neuropsychological measures. These included the Tower of Hanoi (TOH) to investigate executive functions, the FER task for emotional processing, and the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Scale (TEMPS-M) to investigate the affective temperaments. Gray matter volume (GMV) and white matter were estimated using voxel-based morphometry and fractional anisotropy (FA) analysis, respectively.

Source-based morphometry (SBM) was performed to extract structural covariation patterns of GMV and white matter FA. GMV, FA values, and SBM components associated with morphometric and FA differences were compared across BD-I, BD-II, and HC. GMV of cortico-limbic regions implicated in emotional processing was also estimated and their relationship with FER performance investigated using network analysis. To explore the relationships among structural changes, clinical data, executive (TOH) and emotional processing (FER task) measures, correlations analyses were performed.

Results: In the first study, BD-I exhibited reduced GMV in the temporo-insular-parieto-occipital cortex and in the cerebellum compared with HC, whereas no significant differences were found between BD-II and HC nor between BD subtypes. A structural-covariance component encompassing the prefrontal-temporal-occipital network displayed a significant reduction of GMV in BD-I compared to HC, but not between the other groups. Reduced structural network covariance in BD-I was associated with a greater number of manic episodes and worse executive performance. Compared with BD-II, BD-I had an impairment on overall FER performance, which was correlated with lesser temporal-occipital GMV.

In the second study, BD-I displayed the poorest sadness-related FER performance relative to the other groups. In BD-I, sadness-related FER performance was negatively correlated with illness duration and with the number of manic episodes and was positively associated with global functioning.

The overall network structure between GMV and FER performance in both BD subtypes was significantly different compared with HC. BD-I showed a reduced GMV interrelationship in the frontal–insular–occipital regions, as well as a greater edge strength between sadness-related FER performance and amygdala GMV relative to HC.

In the third study, BD-I and BD-II showed significant FA reduction in the same anatomic structures compared with HC. These include the corpus callosum, the cingulum and parahippocampal circumvolution bilaterally, and parieto-occipital regions bilaterally. Of note, BD-II had two clusters

of significantly greater FA located in the genu of the corpus callosum and in the right parahippocampal circumvolution relative to BD-I. Compared with HC, the loadings of FA covariance (IC1), encompassing bilaterally cingolo-callosal-parahippocampal regions, were significantly lower in BD-I, and correlated with TEMPS-M scores. The irritable temperament scores were greater in BD-I versus HC, and were significantly correlated with the IC1 loadings.

Conclusions:

Altered prefrontal-temporal-occipital network structure may reflect a neural signature associated with worse executive functions, as well as impaired emotional processing and illness severity in BD-I. In BD-I, the pattern of reduced interrelationships in the frontal–insular–occipital regions and a stronger positive relationship between the amygdala GMV and sadness-related FER performance may support altered cortical modulation of limbic structures that predisposes to mood instability and emotional dysregulation. Although BD-I and BD-II showed similar FA reduction compared with HC, greater FA in the genu of the corpus callosum and in the right parahippocampal circumvolution can differentiate BD-II from BD-I. In addition, a reduction of cingolo-callosal-parahippocampal FA covariance could represent a structural substrate of higher irritable temperament in BD-I.

Integrating clinical, behavioral, and neuroimaging data, we observed structural and behavioral differences between BD-I and BD-II which support the clinical and nosological differentiation between these subtypes. The identified clinical-behavioral-imaging networks can be targeted for more accurate prognosis and better-tailored clinical interventions for individuals with BD. Future studies with prospective longitudinal designs and larger samples are needed to confirm the present findings and to address inferences about the causal directions of relationships between patterns of abnormal structural network covariance, emotional processing, and affective temperaments in BD.

1. Introduction

Bipolar disorder (BD) is a severe and chronic mental disorder characterized by recurrent episodes of changes in mood, energy levels, sleep, behaviour, and emotional dysregulation (Vieta et al., 2018; APA, 2022: 140, 151-2; Miola et al., 2022a). BD as a distinct nosological entity was first described by Falret and Baillarger in Paris in the 1850s (Angst et al., 2000), although earliest detailed description of manic-depressive illness was made by Heidelberg psychiatrist Emil Kraepelin (Kraepelin, 1921). The main characteristic distinguishing BD from other affective disorders is the presence of recurring manic or hypomanic episodes that may alternate with depressive episodes (Carvalho et al., 2020; Lane & Smith, 2023).

BD type I (BD-I) and BD type II (BD-II) represent the two main subtypes that differ in that manic episodes are selective for BD-I, whereas bipolar depression occurs with both BD-I and BD-II (APA, 2022: 139). Specifically, BD-I is defined by only a history of mania or the presence of mania, with episodes of major depression not being required. Manic episodes are characterized by a wide range of manifestations, including grandiosity, talkativeness, extreme disinhibition, irritability, decreased need for sleep, and highly elevated mood and energy. Psychotic symptoms occur in as many as 75% of manic episodes, with sufficient impairment of psychosocial functioning as usually to require hospitalization (APA, 2022: 140). BD-II is characterized by recurrent depressive and hypomanic episodes, which are less severe and may be briefer than full-blown manic episodes. In addition, cyclothymic disorder remains relatively poorly studied but is defined by recurring depressive and hypomanic states observed over at least two years that do not meet diagnostic requirements for major affective episodes. Finally, there are also other specified bipolar and related disorders, as well as substance-induced and medication-induced bipolar and related disorders; the latter category includes bipolar symptoms, such as mood instability and mania, that are caused by any substance, medication, or medical conditions (APA, 2022: 139, 162, 167).

1.1. Epidemiology

BD affects >1% of the global population, with an estimated lifetime prevalence of 0.6% for BD-I, 0.4% for BD-II, 1.4% for subthreshold manifestations of BD, and 2.4% for a broad bipolar spectrum (Merikangas et al., 2011). Other studies have suggested higher rates. For example, using DSM-IV criteria, the National Comorbidity Study replication found lifetime (and 12-month) prevalence estimates of 1.0% (0.6%) for BD-I, 1.1% (0.8%) for BD-II, and 2.4% (1.4%) for subthreshold BD (Merikangas et al., 2007). These findings were corroborated by a subsequent meta-analysis, revealing a pooled lifetime prevalence of 1.06% (95% confidence interval [95%CI] 0.81-1.31) for BD-I and 1.57% (95%CI 1.15-1.99) for BD-II (Clemente et al., 2015).

A global 12-month prevalence of 1.5% and a lifetime prevalence of 2.1% for BD-I according to DSM-5 criteria have been reported, with no significant differences between men (1.6% and 2.2%) and women (1.5% and 2.0%) (Blanco et al., 2017). Although the prevalence of BD-I is similar in men and women, BD-II is more common in females (Merikangas et al., 2011; Nivoli et al., 2011). Despite regional variation in reported prevalence rates of bipolar spectrum disorder, the severity, impact, and patterns of comorbidity have been remarkably similar internationally (Merikangas et al., 2011).

1.2. Etiopathogenesis

BDs are genetically as well as clinically complex disorders with a multifactorial genesis resulting from genetic and environmental factors (Vieta et al., 2018; Richards et al., 2022). Therefore, a multifactorial model of gene–environment interaction has been hypothesized to best fit this disorder (Vieta et al., 2018).

Although the etiology of BD is unknown, estimates of heritability for BD range from 70% to 90% (Gordovez & McMahon, 2020). Genome-wide association studies (GWAS) provided evidence of a highly polygenic architecture that overlaps with that of schizophrenia (SCZ), major depressive disorders (MDD), and other major psychiatric disorders (Gordovez & McMahon,

2020), following mainly a common disease/common variant model with several genes, each with a small contribution to the risk (Sullivan et al., 2012). Risk genes associated with BD include CACNA1C, CHRNA7, TCF7L2, NCAN, FGF-2, and MAPK1; they belong to pathways involved in neurodevelopment, neuroplasticity, neurodegeneration, and normal brain functioning (Bem et al., 2019; Calabrò et al., 2016; Liu et al., 2014; Wang et al., 2018; Miola et al., 2022b). In this context, the Wnt signaling pathways have been reported to play a key role in the pathogenesis of mood disorders, particularly in BD (Sani et al., 2012; Miola et al., 2022c). Among the key enzymes within this pathway, glycogen synthase kinase-3 beta, responsible for regulating synaptic plasticity, cell survival, and circadian rhythms, has been intricately implicated in both the pathophysiology and treatment of BD (Muneer, 2017; Dandekar et al., 2018).

Several environmental factors, including prenatal and perinatal risk factors, have been implicated in the pathogenesis of BD. Perinatal risk factors include maternal smoking during pregnancy (Talati et al., 2013), cesarean section delivery (Chudal et al., 2014), gestational influenza (Parboosing et al., 2013), and high paternal age (Frans et al., 2008). In this context, a recent review found that peripartum asphyxia (OR = 1.46 [1.02-2.11]), maternal stress during pregnancy (OR = 12.00 [3.30-43.59]), obstetric complications (OR = 1.41 [1.18-1.69]), and birth-weight <2500 g (OR = 1.28 [1.04-1.56]) were associated with an increased risk for BD (Shintani et al., 2023).

Among life events, childhood adversities have classically been implicated as risk factors of BD (Palmier-Claus et al., 2016; Bortolato et al., 2017) and as predictors of a more severe illness-course (Leverich et al., 2002; Agnew-Blais & Danese, 2016; Carbone et al., 2019). Among patients with BD, childhood maltreatment has been associated strongly with early onset of the illness, suicidal ideation and behavior, rapid-cycling course, and substance abuse (Leverich et al., 2002; Daruy-Filho et al., 2011; Duarte et al., 2020; Miola et al., 2023a; Visioli et al., 2023). Some studies also found inferior response to treatments for BD, including lithium, following early mistreatment (Cakir et al., 2016; Etain et al., 2017; Cascino et al., 2021).

Among other factors, drug misuse during adolescence (Tohen et al., 1999), treatment with antidepressants without mood stabilizers (Pacchiarotti et al., 2013), and exposure to treatments including corticosteroids, androgens, electroconvulsive therapy, isoniazid, chloroquine, and tumor necrosis factor-α (TNF-α) inhibitors, have been associated with hypo[manic] mood switches or possible unmasking of latent BD (Goodwin & Jamison, 2007; Miola et al., 2022d). Other medical conditions associated with increased risk of BD include systemic lupus erythematosus, multiple sclerosis, and endocrine disorders, such as Cushing syndrome, hypothyroidism, and Addison disease (Goodwin & Jamison, 2007). Among other environmental risk factors, a previous umbrella review revealed that only irritable bowel syndrome was supported by convincing evidence (OR=2.48 [2.35-2.61]), with asthma and obesity being supported by suggestive evidence, and seropositivity to Toxoplasma gondii and a history of head injury supported by weak evidence (Bortolato et al., 2017). A possible association between hypothyroidism and rapid-cycling course of BD has been reviewed previously (Carvalho et al., 2014; Buoli et al., 2017; Miola et al., 2023a), and a direct association between rapid-cycling course and hypothyroidism was supported only by weak evidence (Miola et al., 2023a).

Among other biological factors, aberrations in the hypothalamic–pituitary–adrenal (HPA) axis, deregulation of mitochondrial function, pathways subserving neuroplasticity or inflammation, and an increase in oxidative and nitrosative stress, as well as epigenetic mechanisms have been proposed to promote neuro-progression in BD (Berk et al., 2011; Belvederi Murri et al., 2016; Post, 2016).

Finally, it has been hypothesized that early neurodevelopmental changes contribute to the pathophysiology of BD, which, together with exposure to postnatal environmental factors during childhood and adolescence, lead to the onset of the disorder in early adulthood (O'Shea & McInnis, 2016; Bortolato et al., 2017). According with a neurodevelopmental hypothesis for BD pathogenesis, indirect evidence suggests that more homogeneous clinical subgroups of BD, especially early-onset BD (<18 years) and BD with psychosis, may be particularly associated with

impaired neurodevelopmental processes (Sigurdsson et al., 1999; Arango et al., 2014). Epidemiological evidence, including perinatal risk factors (Bortolato et al., 2017) as well as evidence from genetic studies, seem to support this hypothesis. For instance, the Wnt pathway has also been reported to be a regulator of crucial processes in the development of the mammalian nervous system and cortical gyrification (Chizhikov et al., 2019). Consistently, a recent review of 14 MRI studies (733 patients with BD, 585 patients with SCZ, 90 with a schizoaffective disorder, and 1380 healthy controls) supports an altered brain gyrification pattern in patients with BD spanning large anatomical and functional neural networks associated with altered cognitive functioning, difficulties in processing and affective regulation, and clinical symptoms (Miola et al., 2022b). However, longitudinal studies are warranted to test associations of different BD phenotypes and pharmacological effects with differences in cerebral gyrification.

1.3. Age of illness onset, delay in diagnosis, and duration of untreated illness

The onset of BD typically occurs at around the age of 20 years (Goodwin & Jamison, 2007), with the peak age at onset of BD being 15–25 years (Scott et al., 2022). A recent study reported that the age of illness onset averaged 7.5 years earlier in individuals with BD than those with MDD (30.7 vs. 38.2 years) and was found to be significantly younger in patients with BD-I than BD-II (Miola et al., 2022e). Among patients with BD, an earlier age of onset has been associated with greater illness severity, including psychotic features (Schürhoff et al., 2000; Azorin et al., 2013), greater suicidal risk, more substance abuse (Carter et al., 2003; Miola et al., 2022e), more mixed episodes (Schürhoff et al., 2000), greater risk of a rapid-cycling course (Carter et al., 2003; Ernst & Goldberg, 2004), inferior treatment response (Schürhoff et al., 2000; Engström et al., 2003), as well as more co-occurring panic and obsessive-compulsive disorders (Schürhoff et al., 2000; Dell'Osso et al., 2009; Azorin et al., 2013; Coryell et al., 2013).

Lack of recognition of previous episodes of mania and especially of hypomania can contribute to frequent delay by several years to establish a BD diagnosis and initiate appropriate treatment,

and such delay may affect outcome adversely. Indeed, a previous meta-analysis identified a pooled estimate for the interval between the onset of BD and the initiation of any form of management of 5.8 years (Dagani et al., 2017), with a recent evidence synthesis quantifying the median delay in diagnosis and duration of untreated BD of 6.7 (IQR: 5.6, 8.9) and 5.9 years (IQR: 1.1, 8.2), respectively (Scott et al., 2022). This is even longer with onset in juvenile years, owing in large part to an excess of depression early in the course of BD (Baethge et al., 2003; Baldessarini et al., 2007). Of note, it is well known that a prolonged duration of untreated illness in BD is associated with more suicide attempts, greater affective and behavioral instability, and possibly more prolonged future illness (Altamura et al., 2010, 2015; Drancourt et al., 2013).

Although subjects initially presenting with a hypo-manic or a manic episode are easily diagnosed as having BD, indeed, an unresolved clinical challenge has been to differentiate individuals presenting with a depressive episode who may eventually meet criteria for BD (Miola et al., 2022e). Although early identification of these cases has been difficult, in some cases it is possible to predict the development of a BD if there is a family history for BD, early age of illness onset, high number of depressive episodes, psychosis, early evidence of impulsivity or subthreshold hypomanic or mixed manic-depressive features, as well as the greater number of suicide attempts (Salvatore et al., 2013; Nestsiarovich et al., 2021; Núñez et al., 2023).

1.4. Bipolar spectrum and main bipolar disorders subtypes

Debates persist regarding the optimal clinical approaches to managing the heterogeneous manifestations behind the broad concept of manic-depressive illness. Some authors favor a dichotomous model of hypomanic and manic syndromes (Parker et al., 2016; Parker et al., 2020; Tondo et al., 2022a, 2022b); others are concerned about the validity of the BD-I vs. BD-II dichotomy based on uncertain distinction of hypomania vs. mania and lack of clear boundaries between the two conditions (Malhi et al., 2019; Gitlin and Malhi, 2020).

Differences between BD-I and BD-II are not limited to the severity of (hypo)manic syndromes, but the BD subtypes differ substantially by several descriptive and clinical measures, and clinical manifestations of BD-II can remain diagnostically stable over many years (Hernandorena et al., 2023). BD-II has been considered as a boundary syndrome between MDD and BD or proposed to lie within a "bipolar spectrum" between BD-II and MDD (Akiskal, 2002). Indeed, depressive episodes are more prominent and long-lasting in people with BD-II compared to those with BD-I (Tondo et al., 2022a). Furthermore, patients with BD-II usually present a higher socio-economic status and better daily functioning than those diagnosed as BD-I, despite often greater long-term morbidity as proportion of time ill (Tondo et al., 2022a). The course of BD-II typically is characterized by depressive onset, early depressive episodes, and depressive predominant polarity, with higher rates of rapid-cycling course of illness at ≥4 recurrences per year (Brancati et al., 2023; Miola et al., 2023a, 2023b). In addition, significantly more additional psychiatric diagnoses but fewer hospitalizations or psychotic features have been found in individuals with BD-II when compared to those with BD-I (Hernandorena et al., 2023). On the other hand, a recent cohort study with data collected prospectively over 4.06 years from 3246 closely and systematically followed adults diagnosed with DSM-5 BD-II (n = 706) or MDD (n = 2540) confirmed that patients with BD-II and MDD differed greatly in many descriptive, psychopathological, and treatment measures (Miola et al., 2023c). Compared with patients with MDD, those with BD-II exhibited a greater risk of familial psychiatric illnesses (including mood disorders and suicide), younger age at illness onset, minor presence of hypomania compared to predominant depression, more education but higher rates of unemployment, nonmarriage or separation, and fewer children, as well as high risks of substance abuse, co-occurring attention-deficit/hyperactivity disorder (ADHD) and general medical disorders, as well as much greater suicidal risk (Miola et al., 2023c).

Despite these clinical distinctions, precise neurobiological mechanisms that differentiate BD-I from BD-II remain a subject of ongoing research. Since the disease expression of BD follows a

multifactorial model, with a strong environmental component and the involvement of both rare and common genetic variants (Almeida et al., 2020), some studies have investigated the genetics of the BD spectrum. The polygenic risk load for BD and SCZ appears greater in BD-I than in BD-II, which is more strongly genetically correlated with MDD, suggesting a different genetic structure of BD generally and in its subtypes (Charney et al., 2017; Mullins et al., 2021). Differences have been found in genes involved in monoaminergic neurotransmitter systems. These include more gene-gene interactions with COMT Val158Met found with BD-II vs. BD-I (Wang et al., 2015), and specific features of GAD1 (glutamate decarboxylase type 1) also associated with BD-II but not with BD-I (Chung et al., 2017). Also, neuroplasticity genes have different polymorphisms and gene-gene interactions between BD subtypes (Rybakowski et al., 2009; Lee et al., 2012). Although a genetic basis of BD-I and BD-II is far from clear, there is growing evidence of a genetic heterogeneity between the BD subtypes (Charney et al., 2017; Richards et al., 2022).

1.5. Co-occurring psychiatric and general medical disorders

Co-occurring psychiatric and general medical illnesses are prevalent in patients and probably contribute to increased mortality (Vieta et al., 2018). Individuals with BD have high rates of coexisting psychiatric conditions, with more than one half of adult patients with BD being diagnosed with at least one lifetime comorbid condition (Loftus et al., 2020). Specifically, these include generalized anxiety disorders (15.1% [95%CI 9.7-21.5]) (Preti et al., 2016), panic disorders (15.5% [11.6-19.9]) (Preti et al., 2018), ADHD (17.11 % [13.05-21.59]) (Schiweck et al., 2021), and substance use disorders (Hunt et al., 2016), such as cannabis use (24% [18-29]) (Pinto et al., 2019) and alcohol use disorders (35.1% [30.3-40.0]) (Di Florio et al., 2014). In addition, a recent report including patients with BD (N = 993,000) found that 12.2% of them have co-existing personality disorders, with borderline personality disorder (8.2%) and antisocial personality disorder (2.6%) being most prevalent (Anona et al., 2024).

Such co-occurring psychiatric disorders make diagnosis and management of BD more difficult and are associated with less favorable outcomes (Merikangas et al., 2007). Indeed, the presence of co-occurring psychiatric disorders in BD has been associated with an earlier onset of BD, a more severe clinical course, poorer adherence to treatment, and greater risk of suicidal behavior (Krishnan, 2005). It is not always clear whether such co-occurrences represent true "comorbidity" (multiple disorders) or another manifestation of the symptomatic complexity of BD itself (Klein & Riso, 1993; Goes, 2023).

Individuals with BD exhibited extremely high rates of co-occurring general medical disorders (96.3%) with at least one medical condition, encompassing cardiovascular, metabolic, endocrine, respiratory, and musculoskeletal systems (Sylvia et al., 2015). These contribute to a shortened life expectancy and premature mortality, as highlighted by a recent meta-analysis which estimated an average of 13 years of potential life lost in individuals with BD compared to the general population (Chan et al., 2022). Among co-occurring cardiometabolic disorders, BD patients are significantly more affected than the general population by obesity and its complications, including type 2 diabetes mellitus (T2DM) (Vancampfort et al., 2015), cardiovascular disease, and metabolic syndrome (Angst et al., 2002; Czepielewski et al., 2013; Giménez-Palomo et al., 2022), with the prevalence of metabolic syndrome in patients with BD being twice compared with that of the general population (Vancampfort et al., 2013). Again, a previous meta-analysis reveals for individuals with BD an almost 1.6-fold increased risk of developing T2DM and equally high obesity risk (RR=1.67, 95% CI 1.32-2.12, $p<0.001$) (Liu et al., 2021). Several factors contribute to such increased risk of obesity and T2DM in people with BD. These include atypical depressive symptoms (hypersomnia, hyperphagia, and psychomotor retardation) (Calkin et al., 2013), sedentary lifestyle, alcohol, and cigarette consumption (Vancampfort et al., 2015), abnormal eating behaviors including binge eating (McElroy et al., 2013, 2016), evening chronotypes (Romo-Nava et al., 2020), as well as adverse effects of BD pharmacotherapy (Burghardt et al., 2018). The pathophysiological commonalities between obesity and T2DM in subjects with BD as

well as current findings of the genetics underlying these complex traits were reviewed recently (Miola et al., 2022c). Of clinical relevance, patients with BD and co-occurring obesity (Fagiolini et al., 2003; Calkin et al., 2009; McElroy et al., 2016; Miola et al., 2022f) or insulin resistance (IR) tend to have less favorable responses to treatment (Calkin et al., 2015; Steardo et al., 2019). A recent review of 10 studies involving nearly 1,200 patients with BD revealed that IR in BD affects specific cognitive domains, including verbal memory and executive functions (Salvi et al., 2020; Chang et al., 2021) and is associated with suggestive hippocampal signatures and prefrontal neurochemical changes (Hajek et al., 2014, 2015). Of clinical relevance, BD patients with comorbid IR/T2DM were more likely to develop a chronic and rapid-cycling course (OR= 2.96, 95% CI 1.69-5.17, OR = 2.88, 95% CI 1.59-5.21, $p < 0.001$, respectively), and exhibited a higher rates of poor clinical response to seemingly adequate mood-stabilizer treatment compared with euglycemic BD patients (k = 2, OR = 6.74, 95% CI 1.04-43.54, $p = 0.04$) (Miola et al., 2023d).

1.6. Factors associated with suicidal behavior

BD is associated with premature mortality, most often owing to suicide (Angst et al., 2002) or cardiovascular disease (Weiner et al., 2011). Suicidal risks are particularly high in patients with BD, especially those who have experienced psychotic or mixed manic-depressive features, or have co-occurring substance abuse, or sufficiently severe MDD as to require hospitalization (Baldessarini et al., 2019; Baldessarini and Tondo, 2020). Among affective disorders, BD carries the highest suicide rate, which is approximately twice that associated with MDD (Gonda et al., 2012; Baldessarini and Tondo, 2020). Patients with BD were nearly four-times more likely to have experienced suicidal acts than those with MDD (Miola et al., 2023e).

Of note, the ratio of attempts/suicides (A/S) is much lower (greater lethality) among those with BD versus MDD patients, indicating that BD not only presents a higher risk of suicidal acts but evidently also that attempts are associated with greater intent to die or more lethal methods (Tondo et al., 2021; Miola et al., 2023e). In 4307 extensively evaluated major affective-disorder

patients with BD (n = 1425) or MDD (n = 2882) followed prospectively for an average of 8.24 years, suicidal risks among study participants diagnosed with BD were much greater than with MDD, but similar with BD-I and BD-II (Miola et al., 2023e).

Associated risk factors included: diagnosis (BD > MDD), family history of suicide or BD, early abuse, separation/divorce, young at illness-onset, manic/psychotic features in first-episodes, female sex with BD, substance abuse, higher cyclothymic, irritable, or dysthymic temperament ratings, greater long-term morbidity, and lower intake functional ratings (Miola et al., 2023e). Based on multivariable logistic regression, five factors remained significantly and independently associated with suicidal acts: BD diagnosis, younger at onset, more time spent in depression during prospective follow-up, lower functional status at intake, and women > men with BD (Miola et al., 2023e). Most factors were similar among BD and MDD participants, though substance abuse, year of birth, and sexual abuse were more prominent or earlier with BD, whereas hospitalization rate, familial suicide, and divorce were greater with MDD (Miola et al., 2023e).

Some reports suggest that suicide attempts in patients with BD are especially likely within the initial years of illness (Tondo et al., 2007; Dome et al., 2019), and can be associated with binge eating behavior, lifetime history of a rapid-cycling course, and younger age at illness onset (Bobo et al., 2018), as well as history of sexual and physical abuses, more hospitalizations for depression, suicidal thoughts when depressed, and cluster-B personality disorder features (Leverich et al., 2003; Zimmerman et al., 2014; Visioli et al., 2023). Of note, a history of suicide attempt and the proportion of time depressed in the past year were significantly associated with suicidal behaviors during the prospective follow-up of 1556 BD participants (Marangell et al., 2006). Finally, in a recent nationwide study including 1673 BD participants, among other risk factors, psychiatric hospitalization within the past year and presence of psychotic symptoms were associated with long-term risk of suicide attempt (Buoli et al., 2022).

1.7. Affective temperaments

As previously mentioned, the latency from initial clinical manifestations to a firm diagnosis and appropriate treatment of BD averages 5–10 years. In this context, it is noteworthy that more than half of those initially diagnosed with MDD ultimately fulfill diagnostic criteria for BD, often due to a missed diagnosis of BD-II through failure to recognize hypomania (Angst et al., 2005). A potential contribution to improving early recognition of BD and MDD might include the use of ratings of affective temperament, seeking potential links between a biological disposition to mood disorder and its clinical manifestations (Gonda et al., 2021). Interestingly, molecular genetic investigations revealed a strong involvement of the central serotonergic (depressive, cyclothymic, irritable, and anxious temperaments) and dopaminergic (hyperthymic temperament) regulation, suggesting that the genetic potential of major mood episodes lies in these temperaments (Rihmer et al., 2010). Therefore, affective temperament types (hyperthymic, depressive, irritable, cyclothymic, and anxious) are conceived as subclinical (trait-related) manifestations and, acting as a bridge between genes and clinical manifestations, could represent vulnerability factors and precursors of major mood disorders (Akiskal and Akiskal, 2005; Evans et al., 2005; Rihmer et al., 2010; Fountoulakis et al., 2016). Moreover, temperaments may constitute illness course modifiers influencing the clinical expression as well as significantly affecting the long-term course and prognosis of BD (Rihmer et al., 2010; Azorin et al., 2011; Iasevoli et al., 2013; Serra et al., 2017; Miola et al., 2021). In addition to supporting earlier and more accurate diagnoses, the study of affective temperaments may also have predictive value for suicidal behavior or ideation (Vázquez et al., 2018; Miola et al., 2023e). There is also preliminary evidence that temperament assessments may help predict response to antidepressant or mood-stabilizing treatments (De Aguiar Ferreira et al., 2014).

Previous evidence suggests that hyperthymic and depressive temperaments are related to a more ‘classic’ bipolar picture, while cyclothymic, anxious, and irritable affective temperaments are related to more complex features and might predict poor response to treatment, violent or

suicidal behavior, and higher odds of comorbidity (Fountoulakis et al., 2016). In this context, a study analyzing data collected over 7.99 years from 858 individuals diagnosed with a DSM-5 major affective disorder revealed thorough multivariable logistic regression modeling that higher scores for cyclothymic and irritable temperaments were independently more likely among patients with BD than those with MDD, whereas dysthymic and anxious temperament scores were higher in patients with MDD than those with BD (Miola et al., 2021). Moreover, this report confirmed associations of suicidal risk with higher scores of all temperament types except for hyperthymic, which were lower, as had been shown previously (Pompili et al., 2018; Tondo et al., 2018; Vázquez et al., 2018). Other noteworthy findings included higher cyclothymic and irritable scores and lower anxious scores with substance abuse, especially among patients with BD (Miola et al., 2021). Second, higher ratings for dysthymic temperament have been correlated strongly with the proportion of time in depression within both patients with BD and MDD, whereas higher ratings for irritable temperament significantly correlated with the proportion of time spent in mania or hypomania among patients with BD. Finally, higher scores for cyclothymia correlated significantly with %-time-ill and episodes/year but only among BD subjects (Miola et al., 2021). Cyclothymic temperament has been associated with a relatively unfavorable prognosis, perhaps as reflecting emotional and behavioral instability (Miola et al., 2021, 2023c). This view is in line with previous reports showing that higher ratings of cyclothymic temperament can affect illness course unfavorably (Nilsson et al., 2012; Innamorati et al., 2015). Consistently, high cyclothymia scores in BD have been reported to predict an excess of affective recurrences, even when controlling for medication non-adherence (Nilsson et al., 2012). Additionally, high cyclothymia ratings have been associated with poorer treatment adherence and response to medication (Fornaro et al., 2013; Buturak et al., 2016) or to psychoeducation (Reinares et al., 2020).

Although affective temperaments seem to play a crucial role in BD, representing behavioral and biological intermediate phenotypes that can affect the clinical presentation of BD (Perugi et

al., 2012), the neurobiological underpinnings of affective temperaments in individuals with BD remain poorly understood.

1.8. Affective cognition, emotional dysregulation, and emotional processing

Alterations in "cold" cognition are well documented in BD (Cullen et al., 2016), with more severe and widespread impairments in patients with BD-I than those with BDII (Cotrena et al., 2020). In addition, there has been a growing interest in investigating impairments in affective cognition within individuals with BD. Affective cognition is considered to be part of "hot" (emotion-laden) cognitive processes and includes measures of emotional regulation, emotion processing, perceptual and attentional biases, feedback sensitivity, emotional decision-making, and reward and punishment processing (Roiser & Sahakian, 2013; Cotter & Barnett, 2018; Miskowiak et al., 2019). Impairments in affective cognition have been increasingly recognized as a core feature of BD, representing part of the neurocognitive profile, a candidate endophenotype (Vierck et al., 2015; Miskowiak et al., 2017), and promising treatment targets in BD (Miskowiak et al., 2019). Of note, affective cognition also predicts psychosocial function and quality of life in individuals with BD. Specifically, impairments in affective cognition, including emotional intelligence and regulation, seem to have a negative impact on interpersonal and psychosocial functioning in BD (Ryan et al., 2013; Aparicio et al., 2017), as well as an indirect effect on psychosocial functioning via an influence on depressive symptoms (Van Rheenen & Rossell, 2014). On the other hand, better affective cognition has been associated with favorable functional outcomes and quality of life in BD (Fulford et al., 2014).

Emotional dysregulation

Emotional dysregulation (ED) is increasingly considered a core psychological mechanism in BD, leading to maladaptive strategies in response to emotional distress (Gratz and Roemer, 2004), which could potentially underlie affective symptoms (Dodd et al., 2019).

Specifically, ED is widely acknowledged as a multidimensional and transdiagnostic phenomenon (Cludius et al., 2020). It encompasses challenges related to the control of impulsive behaviors, regulation of emotional responses to negative stimuli (Gratz and Roemer, 2004), and heightened levels of affective instability, often accompanied by a delayed return to an emotional baseline (Ebner-Priemer et al., 2015). Patients with BD, influenced by traumatic early life experiences, personality traits, or neurobiological factors, appear to be particularly susceptible to experiencing difficulties in effective emotional regulation (ER) (Koenders et al., 2020).

Since a universally agreed-upon definition of ED remains elusive (D'Agostino et al., 2017), numerous tools have been developed, each emphasizing specific facets of ED. These include the Response to Positive Affect (RPA) scale (Feldman et al., 2008), the Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski & Kraaij, 2007), the Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003), and the Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004).

The DERS, the most widely used scale to assess ER in both clinical and research settings, is a 36-item assessment questionnaire that explores subjective emotion ability and quantifies challenges in regulating negative emotions (Gratz & Roemer, 2004; Hallion et al., 2018).
Using the DERS scale, a recent evidence synthesis provides quantitative evidence of differences in ER strategies between patients with BD and healthy controls (HC), as well as between patients with BD and those affected by borderline personality disorder (BPD) (Miola et al., 2022a). This meta-analysis revealed that patients with BD present significantly greater difficulties in ER than HC. Moreover, the latter work confirmed the crucial role of ED in the pathophysiology of BD and BPD, with a large effect size for the impairment in domains exploring the access to ER strategies and impulsive behaviors in BPD (Miola et al., 2022a). Again, another systematic review and meta-analysis confirmed that patients with BD significantly differed from HC in relying on more maladaptive ER strategies, such as negative focus, rumination, risk-taking behaviors. Interestingly, first-degree relatives seem to present similar alterations compared to fully

syndromic individuals with BD, supporting the idea that ED could be partly heritable and may span a continuum (De Prisco et al., 2022).

Of clinical relevance, ED appears to be associated with heightened severity in both manic and residual depressive symptoms among individuals with BD (Rucklidge, 2006). Moreover, mounting evidence suggests that individuals with BD exhibit tendencies toward excessive upregulation and downregulation of both positive and negative affect, even during remission (Townsend and Altshuler, 2012; Dodd et al., 2020). Given its established linkages with disruptions in circadian rhythmicity, sleep disorders, and suicidal behavior (Palagini et al., 2019), ED may also exacerbate the clinical course of BD. This, together with impairment in psychosocial functioning and overall quality of life (Hoertnagl et al., 2011; Van Rheenen & Rossell, 2014) among affected individuals, calls for the development and implementation of targeted treatment strategies (Dadomo et al., 2016). In addition, despite the evident clinical relevance of ED in BD, the neurobiological bases underlying ED in BD remain poorly understood. Previous neuroimaging investigations provided evidence of changes in brain activity patterns in patients with BD compared to HC involving several regions implicated in emotion processing. These include the amygdala, insula, thalamus, hippocampus, and prefrontal cortex, with these alterations being observed in patients with BD during mood episodes and in euthymic phases, but also in individuals at risk for the disorder (Chen et al., 2011; Townsend & Altshuler, 2012; Phillips & Swartz, 2014; Corbalan et al., 2015; Sepede et al., 2015; Cattarinussi et al., 2019; Bertocci et al., 2020). Furthermore, in a recent meta-analysis of 21 functional MRI (fMRI) studies, ALE maps for emotion-related tasks revealed hyperactivation in the caudate, amygdala, precentral gyrus, middle frontal gyri, and sub-gyrus, whereas hypoactivation in the inferior frontal and anterior cingulate gyrus emerged in patients with BD (Ahmed et al., 2023). Although impairments within the fronto-limbic circuits are believed to be crucial factors underlying the ER challenges observed in individuals with BD (Mesbah et al., 2023), there is an urgent need for research efforts shedding light on the complex interplay between neural mechanisms and ER in BD (Miola et al., 2022a).

Facial Emotion Recognition (FER)

Among the affective cognition domains, the most consistent trait-related impairments in BD are facial emotion (expression) recognition (FER) and implicit emotion regulation, as underscored by the International Society of Bipolar Disorder (ISBD) Targeting Cognition Task Force (Miskowiak et al., 2019).

FER, which is the ability to identify emotional states from facial expressions, plays a pivotal role in social interaction and communication (Rocca et al., 2009). FER impairment can disrupt interpersonal relationships and act as a determinant of the decline in daily functioning (Vlad et al., 2018). Notably, FER is reported to be altered in many psychiatric disorders. In this context, a recent review found that patients with BD are more accurate than those with SCZ in identifying each type of emotion during a FER task, with specific differences in the perception of anger, fear, and sadness. On the other hand, those with BD were less accurate in identifying emotions than people with MDD, and these differences were more specific for sad emotional stimuli (De Prisco et al., 2023).

The impairment of emotional processing in BD has been proposed as moderate and stable, as well as a possible endophenotype and trait marker of BD (Derntl & Habel, 2011; Kohler et al., 2011). Indeed, a previous report investigating emotion recognition in unaffected relatives of BD patients revealed that the offspring of these patients were worse than the matched HC in labeling sad and angry faces; in addition, symptomatic children at high risk for BD made more errors than asymptomatic children in labeling sad but not angry or fearful faces (Hanford et al., 2016).

Notably, several studies have reported that individuals with BD exhibit a general deficit in FER, as indicated by decreased accuracy and/or prolonged response times (Bozikas et al., 2006; Hoertnagl et al., 2011; David et al., 2014; Miola et al., 2022g). Conversely, other research has pointed to selective impairments, specifically in the recognition of individual emotions (Martino et al., 2011; Altamura et al., 2016; De Brito et al., 2016; Branco et al., 2018), and the processing

of sadness emerged as a particular alteration in ER associated with BD. Again, a previous meta-regression analysis has shown significant associations between the proportion of BD-I patients and accuracy of labeling of happiness and sadness faces (Samamé et al., 2015).

Several investigations have delved into the link between mood states and FER in individuals with BD. Notably, manic patients have shown impairments in sadness-related FER performance, and these impairments intensified as emotional intensity increased. These findings have been associated with altered activation patterns within the limbic and frontal circuits that are central to facial emotion processing (Lennox et al., 2004; Chen et al., 2006). Furthermore, when compared to both depressed patients with BD and controls, manic BD patients displayed hyperactivation in the fusiform gyrus in response to sad facial expressions (Chen et al., 2006). Conversely, individuals experiencing depression in both MDD and BD tend to exhibit a mood-congruent bias. This bias manifests as a tendency to misinterpret neutral expressions as sad and happy expressions as neutral, with the severity of depression having an impact on overall FER performance (Gur et al., 1992). Interestingly, during depressive episodes, patients with BD exhibited heightened activation in the hippocampus when processing mild facial expressions of sadness, in contrast to HC and those with MDD (Lawrence et al., 2004).

The brain network implicated in FER is composed of several brain regions. These include hippocampus, implicated in the recall and regulation of emotional memories (Haxby et al., 2002; Femenía et al., 2012); amygdala, involved in arousal by negative emotions (Gur et al., 2002; Haxby et al., 2002); insula, responsible for modulation of the arousal level (Haxby et al., 2002); anterior cingulate cortex, with a role in linking reward and punishment processing (Gur et al., 2002; Haxby et al., 2002; Rolls, 2019); fusiform gyrus, responsible for the recognition of the invariant aspect of face processing (Gur et al., 2002; Haxby et al., 2002); and prefrontal cortex (PFC) implicated in the integration of emotion and cognition (Gur et al., 2002; Beer et al., 2006; Miola et al., 2023f).

1.9. Neuroimaging correlates of bipolar disorder versus healthy controls

Neuroimaging has emerged as a valuable tool for investigating the neural substrates of psychiatric disorders, with previous literature suggesting alterations both in structural and functional neuroimaging in BD when compared with HC. A recent whole-brain voxel-based morphometry (VBM) meta-analysis found that people with BD show decreased volume in the right inferior frontal gyrus, including the right insula, superior temporal gyrus, left superior temporal gyrus extending to the left insula, temporal pole, and inferior frontal gyrus, anterior cingulate cortex, left superior frontal gyrus, left thalamus, and right fusiform gyrus (Chen et al., 2022). Studies on large-size samples conducted by the worldwide consortium ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) demonstrated significant cortical abnormalities, with BD patients presenting a thinner grey matter cortex in frontal, temporal, and parietal regions in both the hemispheres (Hibar et al., 2018). Other studies found volume differences in subcortical structures, with people with BD showing a reduced volume in the hippocampus and thalamus, with wider lateral ventricles (Hibar et al., 2016). Again, a recent systematic review of 14 MRI studies (733 patients with BD, 585 patients with SCZ, 90 with a schizoaffective disorder, and 1380 healthy controls) supports an altered and heterogeneous brain gyrification pattern in individuals with BD encompassing large anatomical and functional neural networks associated with clinical symptoms as well as with impaired cognitive functioning, altered emotional processing and emotion dysregulation (Miola et al., 2022b). Moreover, diffuse tension imaging (DTI) studies revealed a decreased mean fractional anisotropy (FA) in people with BD when compared with HC; this difference was more evident in the corpus callosum and cingulum and underscored an altered white matter integrity and connectivity in BD (Favre et al., 2019). Notably, functional neuroimaging studies reported abnormal brain activity both in resting-state and task-based MRI. Studies on resting-state functional connectivity showed a large-scale network dysfunction in the acute phase compared to the remitted state of BD, with BD patients presenting decreased connectivity within the affective network (AN) and the default-mode network (DMN)

during mood episodes (Wang et al., 2020). Condition-dependent functional neuroimaging studies found altered activity in the left amygdala during emotional experiments and in the left superior and right inferior parietal lobules, with increased activity in the left medial orbitofrontal cortex during cognitive tasks (Schumer et al., 2023). Lastly, a recent meta-analysis showed hyperactivation in the ventromedial prefrontal cortex and subgenual anterior cingulate cortex during working memory and increased activity in the orbitofrontal cortex during reward processing in BD versus HC (Mesbah et al., 2023).

2. Structural and functional correlates associated with bipolar subtypes: state of the art of neuroimaging studies

In recent years, neuroimaging studies have played a pivotal role in unraveling neural correlates of BD subtypes, offering insights into the potential structural, functional, and connectivity differences that contribute to their clinical presentations. However, to date, there has been no comprehensive synthesis of the neuroimaging literature systematically comparing BD-I and BD-II. Therefore, this chapter aims to bridge this gap by providing a thorough examination of the neuroimaging studies that have investigated the differences between BD-I and BD-II. By synthesizing findings from a diverse array of neuroimaging approaches, including structural magnetic resonance imaging (MRI), functional MRI (fMRI), and diffusion tensor imaging (DTI), this chapter aims to provide a comprehensive overview of the neural signatures underlying the main BD subtypes.

Methods

Search Strategy

A comprehensive literature search was conducted to identify peer-reviewed articles investigating neuroimaging differences between BD-I and BD-II. The comprehensive search was performed across two databases (PubMed and Scopus) without any language restriction, from inception to December 6, 2022, using the following search strategy: "(Bipolar disorder OR BD OR bipolar disorder type I OR bipolar disorder type II OR BD-I OR BD-II) AND (sMRI OR structural magnetic resonance imaging OR VBM OR voxel-based morphometry OR SBM OR surface-based morphometry OR cortical thickness OR gyrification OR GI OR sulcal depth OR fractal dimension OR FD OR DTI OR diffusion tensor imaging OR white matter abnormalities OR tract-based spatial statistics OR TBSS OR white matter hyperintensities OR WMH OR functional MRI OR fMRI OR functional neuroimaging)." Reference lists of identified studies were also searched manually.

Eligibility and Study Selection

Studies were considered eligible if they met the following criteria: (1) carried out in humans, (2) focused on neuroimaging comparisons between BD-I and BD-II groups, (3) included adult participants diagnosed with either BD-I or BD-II according to standardized diagnostic criteria, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), (4) utilized structural magnetic resonance imaging (MRI), functional MRI (fMRI), or diffusion tensor imaging (DTI) techniques, and (5) provided sufficient data for the comparison of neuroimaging findings between the main BD subtypes, (6) case–control, experimental, cross-sectional and prospective studies were considered eligible. Commentaries, case reports, editorials, letters to the editors, and reviews were excluded.

Data Synthesis and Analysis

Due to the heterogeneity of methods and data-reporting, a narrative synthesis approach was chosen to summarize the findings. Extracted data were summarized and categorized according to different neuroimaging modalities (e.g., structural MRI, functional MRI), highlighting reported differences between BD-I and BD-II groups. Themes and patterns emerging from the reviewed studies were addressed to provide insights into neurobiological distinctions between the BD-I and BD-II subtypes.

Results

A total of 4240 studies were identified from Scopus and Pubmed databases. After duplicate removal, 3095 abstracts were selected, of which 43 articles were retrieved for full-text assessment. A total of 33 studies plus two additional reports found in reference lists of screened reports were included. Overall, this chapter included 39 experiments (four studies included more than one measure): five functional magnetic resonance, 11 white matter, and 23 structural magnetic

resonance imaging experiments. Most of the studies (n = 12) were conducted in Western Europe, nine in South-East Asia, eight in the USA, four were international multisite studies, and two were from Australia.

1. Structural MRI

1.1 ROI based

Regarding the differences in frontal and temporal structures between patients with BD-I and BD-II, two studies (Gutiérrez-Galve et al., 2012; Yang et al., 2021) investigated volumetric differences in regions belonging to the frontal lobes; one limited its analysis to the temporal lobes (Brambilla et al., 2003), and another investigated temporal lobes and hippocampus (Hauser et al., 1999). Yang et al. 2021 found no significant volumetric difference between BD-I and BD-II. However, when patient groups were compared to HC, BD-I showed lower gray matter volumes in the left inferior temporal gyrus, left temporal pole, and bilateral rostral middle frontal gyrus, whereas patients with BD-II exhibited lower gray matter volumes in regions of the left temporal lobe. Gutiérrez-Galve et al. 2012 studied the cortical thickness (CT), surface area, and volume of six frontal and six temporal ROIs, and found no significant difference between BD-I and BD-II in total brain volume, in frontal or temporal CT or surface area, or in the strength of the association between premorbid IQ, memory and executive functions, and frontal cortical measures. Brambilla et al. 2003 focused their analysis on a variety of temporal structures; they found that the left amygdala was significantly larger in patients with BD than in HC, with no significant difference between small samples of BD-I (n=18) and BD-II (n=6) patients. Hippocampus, superior temporal gyri, and temporal lobe volume also showed no significant differences between BD and HC, nor between BD-I and BD-II (Brambilla et al., 2003). Conversely, Hauser and colleagues found that patients with BD-I had significantly larger lateral ventricle area and the lateral ventricle to cerebrum (LV/C) area ratio in the left hemisphere than those with BD-II or HC, with such

measures being approximately twice as large in the BD-I group as in the other groups (Hauser et al., 1999).

Regarding possible differences in the hippocampi, three other studies (Cao et al., 2017; Janiri et al., 2019; Haukvik et al., 2022) specifically investigated hippocampal volume differences between BD subtypes. Janiri et al. 2019 performed a VBM study on some hippocampal subfields (CA1, CA2/3, CA4/dentate gyrus, presubiculum, and subiculum) for both hemispheres, and found no significant differences between BD-I and BD-II. However, compared to HC, patients with BD-I and BD-II both presented lower volumes in all hippocampal subfields. Similarly, Haukvik et al. 2022 found no significant differences for whole hippocampus or any of its subfields between BD-I and BD-II. Also, when compared to HC, BD-II showed no difference in whole hippocampus volume, whereas BD-I presented lower whole hippocampal volumes, which sustained across most subfields, including the hippocampal tail, subiculum, presubiculum, CA1, CA2/3, CA4, molecular layer, granule cell layer of the dentate gyrus (GC ML DG), and the hippocampal amygdala transition area. Consistent with the previous findings, Cao et al. 2017 identified lower hippocampal volumes in people with BD compared to HC, and further post hoc *t*-tests within BD subtypes revealed that this difference was driven mainly by BD-I patients, with no significant difference in hippocampal subfield volumes in participants with BD-II compared to HC.

Other studies investigated subcortical motor control areas. Among these, Brambilla et al. 2001 performed an anatomical MRI study of basal ganglia in patients with BD, and found that caudate, putamen, and total globus pallidus volumes, after correction for ICV, were not significantly different between BD and HC. However, in patients with BD-I the duration of illness influenced to a greater extent basal ganglia volumes than BD-II, with a negative correlation (longer duration of illness associated with lower volumes) in right caudate, right putamen, and left putamen, and a positive correlation with left globus pallidus.

Regarding the cerebellum, two studies (Kim et al., 2020; Olivito et al., 2022a) investigated morphological features of this structure in BD. Olivito et al. 2022a found a significant cerebellar

atrophy in both BD-I and BD-II when compared to HC, with a more diffuse involvement in BD-II than BD-I, and with both patient groups showing atrophy in the right lobule I-IV, V, Crus I and Crus II and the left Crus II and vermis Crus II. Similarly, Kim et al. 2020 found a smaller cerebellar volume in BD versus HC, which was limited to the left lobule IX. Furthermore, the same authors found a significant increase in the CT of all cerebellar subregions in the BD group compared to HC, with the comparison between BD-I and BD-II showing no significant differences in cerebellar CT or subregional volumes.

1.2 Whole brain

1.2.1. Voxel-based morphometry (VBM)

Five studies adopted a whole-brain, VBM approach to compare structural differences between BD subtypes (Ha et al., 2009; Caseras et al., 2013; Maller et al., 2014, 2015; Miola et al., 2022g). Comparing patients with BD-I and HC, Miola et al. 2022 found decreased gray matter volume in clusters scattered bilaterally in the superior, middle, and inferior temporal gyri, in the right middle and inferior occipital gyrus, right insula, left inferior parietal lobule, and cerebellar culmen, with no significant differences between BD-I and BD-II nor between BD-II and HC (Miola et al., 2022g). When considering the differences between patients with BD-I and BD-II, Caseras et al. 2013 found that patients with BD-II had significantly greater left putamen volume than patients with BD-I, and that the volume of this structure correlated positively with left ventral striatal activity during reward anticipation tasks. On the other hand, Ha et al. 2009 found that patients with BD-II and BD-I exhibited gray matter deficits in the ventromedial prefrontal regions, compared to HC, and that BD-I patients also displayed widespread lower volumes of gray matter bilaterally in frontal, temporal, parietal and parahippocampal cortices, compared to HC. However, the gray matter volume reductions encompassing frontal, temporal, and posterior cingulate regions found in BD-I versus BD-II ($p < 0.001$, uncorrected), did not survive FDR correction. Interestingly, age of onset negatively correlated with the gray matter concentrations in the

bilateral medial orbitofrontal gyrus of patients with BD-II, whereas age of onset, illness duration, and depressive symptoms did not correlate with any regional volume in patients with BD-I (Ha et al., 2009). Maller et al. in 2014 and then in 2015 focused on differences between patient groups in gray matter and white matter using the VBM approach. Maller et al. 2014 reported that BD-I patients had less cortical volume and cortical thickness in the right medial orbitofrontal region, and a reduction in cortical thickness also in the left superior temporal gyrus. Later, Maller and colleagues (2015) compared BD-I versus BD-II patients and found no gross volumetric differences but an increased ratio of total brain volume (TBV) to intracranial volume (ICV) among females with BD-I compared with females with BD-II. Patients with BD vs. controls showed a decreased total gray matter volume but no significant differences in total brain volume, white matter volume, or the ratio of TBV to ICV (Maller et al., 2015).

1.2.2. Surface-based morphometry

Surface-based morphometry can be employed to study the cortical structure of the brain, and some studies, based on the background of cortical or gyrification alterations in affective disorders, evaluated the brain surface to highlight differences between patients within the BD spectrum. A general decrease in cortical thickness was found in seven studies that compared BD with HC. Thinner cortical regions were more frequent in patients with BD-I than BD-II, sometimes with a decrease in surface area that suggested altered brain gyrification (Lyoo et al., 2006; Abé et al., 2016, 2018, 2021; Hibar et al., 2018; Woo et al., 2021; Mcwinney et al., 2022).

In 2006, Lyoo and colleagues described significant decreases in CT in multiple cortical areas, including the left cingulate cortex, left middle frontal cortex, left middle occipital cortex, right medial frontal cortex, right angular cortex, right fusiform cortex, and bilateral postcentral cortices in patients with BD versus HC. However, there were no significant differences in CT for any ROIs between subjects with BD-I (n=18) and with BD-II (n=7), although these small samples may be underpowered to detect significant differences within BD subtypes (Lyoo et al., 2006).

Abé et al. 2016 found that patients with BD-I had significantly lower CT than those with BD-II in the right temporal lobe, with lower cortical thickness also in a large cluster of medial frontal regions that did not survive correction for multiple comparisons. When comparing BD-I to HC, the first exhibited less CT in left and right frontal and temporal regions, insula, pre- and postcentral regions, and medial occipital lobe with visual areas. Those with BD-II had lower CT than HC in left and right frontal and temporal regions and in the medial occipital regions, involving smaller clusters than those observed in the comparison between patients with BD-I and HC (Abè et al., 2016). Similar to the BD-I group, regions in which significant differences in cortical thickness have been found were similar to regions with differences in cortical volume and/or area. Later, in 2018, Abé et al. found that CT differences between BD-II and HC mainly involved right medial prefrontal regions and left medial occipital regions. In addition, patients with BD-II differed from patients with BD-I in the degree of CT in the right lateral prefrontal area. Moreover, there was a positive correlation between cognitive performance (based on a neuropsychological test battery exploring executive functions) and CT of the right medial superior frontal regions, the bilateral inferior precentral cortex, the bilateral medial occipital regions, and lateral prefrontal cortex of patients with BD-II. On the other hand, for patients with BD-I, such a positive correlation was evidenced only for a small cluster belonging to the left lateral superior frontal cortex.

Interestingly, a multicenter longitudinal sMRI study conducted by the ENIGMA BD Working Group identified thickness differences in limbic areas between the BD-I and BD-II groups, particularly in the right parahippocampal gyri, with patients with BD-I showing a decline in right parahippocampal thickness, whereas those with BD-II displayed thickness increases in the same region (Abé et al., 2021). Of note, a decreased surface area affecting the right insula was described by Woo et al. 2021 in patients with BD-II when compared to those with BD-I. Moreover, patients with BD-I showed thinner cortical regions than those with BD-II and HC in the pars triangularis, left pars opercularis, and right pars orbitalis of the inferior frontal gyrus and in the right orbital

gyrus. However, the left pars orbitalis showed significant cortical thinning in patients with BD-II but not in patients with BD-I. Lastly, Hibar et al. 2018 found no significant differences in CT or surface area between patients with BD-I or BD-II (Hibar et al., 2018). Notably, the authors evidenced a significant association between the duration of illness and cortical thickness, which might also interact with medication status.

2. White matter

Two studies examining white matter abnormalities in individuals with BD yielded different results. Ambrosi et al. (2016) observed increased Fractional Anisotropy (FA) in the right inferior longitudinal fasciculus (ILF) in patients with BD-I compared to those with BD-II, whereas Ha et al. (2011) reported the opposite trend. On the contrary, Liu et al. (2010) found increased FA values in BD-I in the right precuneus, right inferior frontal gyrus, and left inferior prefrontal area compared to BD-II. Maller et al. (2014) observed a trend toward increasing Mean Diffusivity (MD) in several brain regions, including brain stem, internal capsule, middle temporal gyrus, putamen, and thalamic radiation, with consistently higher values in BD-I than BD-II. Additionally, Radial Diffusivity (RD) was increased in patients with BD-I compared to BD-II in the insular area. The same authors (Maller et al., 2015) later studied occipital bending in patients with BD and found an increased prevalence of this alteration among BD patients (irrespective of subtype) than in HC.

Ha et al. (2011) also studied Mean Apparent Diffusion Coefficient (ADC) maps, revealing lower ADC values in specific regions of patients with BD-I compared to BD-II in left frontal, right parietal, temporal regions, and right thalamus.

Two other studies (Squarcina et al., 2017; Kieseppä et al., 2022) included a comparison group with a different psychiatric diagnosis along with patients with BD. Squarcina et al. (2017) found that both BD and SCZ groups showed decreased FA and increased MD, volume ratio (VR), axial diffusivity (AD), and RD when compared to HC, with overlapping affected areas in both BD and

SCZ. However, there were no significant differences in diffusion indices between BD and SCZ nor between BD-I and BD-II. Kieseppä et al. (2022), investigating DTI changes and White Matter Hyperintensities (WMHs) in BD and MDD, found decreased FA in the corpus callosum in BD-I and in the right cerebellar middle peduncle in MDD, with no significant diffusion index changes in BD-II compared to HC. Patients with BD-I showed DWMHs mainly in the right frontal lobe, whereas patients with BD-II and MDD showed them in the right and left frontal lobes and basal nuclei, and in the left frontal lobe, respectively. Tighe et al. (2012) studied WMHs and observed a positive linear trend in the mean total WMH volume when comparing HC, unaffected individuals, patients with BD-II, and patients with BD-I with and without a history of psychotic symptoms.

Two studies (Caseras et al., 2015; Foley et al., 2018) specifically focused on white matter tracts. Foley et al. (2018) found lower FA in both the left and right uncinate fasciculus in patients with BD-I compared to BD-II and HC, with no difference between BD-II and HC. Caseras et al. (2015) observed the same difference, but only in the right uncinate fasciculus. The same authors also studied longitudinal and radial diffusivity (RD), finding an increase in RD in patients with BD-I compared to BD-II and HC. Foley et al. (2018) also investigated the cingulum body and parahippocampal cingulum but found no significant differences among the three groups. Lastly, a previous prospective study investigating signal hyperintensities in three brain regions (periventricular white matter, subcortical gray matter, and deep white matter) among treatment-refractory patients with BD, revealed that those with BD-I over age 30 had a significantly greater frequency of periventricular WMHs than HC and those with BD-II, with no significant differences between BD-II and HC (Altshuler et al., 1995).

3. Functional neuroimaging

Five studies using functional MRI techniques were eligible to be included in this review. Caseras (2013, 2015) carried out two task-based investigations concerning emotion regulation and reward

anticipation. Caseras et al. 2013, during the reward anticipation task, found that patients with BD-II showed greater bilateral ventral striatal activity than HC and those with BD-I. Interestingly, the authors evidenced that patients with BD-II had significantly greater left putamen volume than those with BD-I, with the left putamen volume being correlated positively with left ventral striatal activity to reward anticipation in all participants. Caseras et al., 2013 also conducted a whole-brain level analysis which showed greater activity in the left ventrolateral prefrontal cortex, insula, precentral gyrus, and middle and superior temporal cortex of patients with BD-II relative to BD-I and HC. BD-II patients also exhibited greater activity than HC in the caudate nuclei bilaterally and the left dorsolateral prefrontal cortex, while no significant differences emerged between BD-I and HC.

In a 2015 study by the same authors, Caseras and colleagues combined a neuroimaging emotion regulation paradigm with an anatomical diffusion-weighted scan to study the amygdala, accumbens, and frontal activity. Participants were administered a mixed event–block design verbal n-back task with the possible presence of distractors with emotional valence. Slowed reaction times to targets were shown with both increasing memory load and the presence of emotional distracters, predominantly in patients with BD-I. When fear distracters were administered, both patients with BD-I and BD-II showed increased activity in the amygdala, accumbens, and dorsolateral prefrontal cortex, with respect to HC. When comparing BD-I and BD-II, the latter exhibited an increased activation localized to the dorsolateral prefrontal cortex (DLPFC) and amygdala. In the presence of happy distracters, BD-I showed increased activity in all three ROIs compared to HC and BD-II. Conversely, BD-II presented increased activity compared to HC only in the amygdala. When neutral distracters were in place, HC showed increased activity in the DLPFC compared to BD-I, and lower activation in the amygdala and accumbens (Caseras et al., 2015). To summarize, patients with BD-I displayed abnormalities in functional and anatomical connectivity between prefrontal cortices and subcortical structures in emotion regulation circuitry, whereas such deficits did not extend to those with BD-II. According

to the authors, these findings, along with the altered white matter microstructure organization in the right uncinate fasciculus in patients with BD-I compared with BD-II (see above), support crucial differences in the pathophysiology of BD subtypes.

Regarding resting-state functional studies, Liu et al. 2022 conducted a whole brain analysis computing the dynamic amplitude of low-frequency fluctuation (dALFF), showing that patients with BD displayed widespread lower dALFF values, mainly in the frontal, parietal, and temporal cortices. Of note, a significant decrease in dALFF values emerged in the right superior and middle temporal gyrus in patients with BD-I compared with BD-II, suggesting potential differential diagnostic neuroimaging biomarkers for BD subtyping.

Two fMRI studies performed seed-based functional connectivity (FC) analyses (Olivito et al., 2022b; Wei et al., 2022). Wei et al. 2022 performing a caudate-seeded FC study, revealed that patients with BD-I had significantly decreased FC between the DC and the orbitofrontal cortex (OFC) as compared to those with BD-II, and between the DC and the putamen and parahippocampal gyrus as compared with HC. Patients with BD-II exhibited decreased FC between the DC and the OFC, ventrolateral prefrontal cortex, DLPFC, posterior parietal cortex, inferior temporal gyrus, parahippocampal gyrus, supplementary motor area, thalamus, pons, and cerebellum as compared with the HC group. Finally, Olivito et al. 2022b exploring the cerebellar-cerebral FC found no significant differences in dentate-cerebral FC between those with BD-I and BD-II. Still, patients with BD-I and BD-II showed an altered pattern of cerebello-cerebral FC involving both left and right dentate nucleus when compared with HC.

4. Patient comorbidities in the included studies

Most of the studies applied common neurological exclusion criteria for neuroimaging studies, such as: a history of head trauma with subsequent loss of consciousness, the presence of neurological disease (Lyoo et al., 2006; Ha et al., 2009, 2011; Gutiérrez-Galve et al., 2012; Maller et al., 2014, 2015; Squarcina et al., 2017; Cao et al., 2017; Janiri et al., 2019; Choi et al., 2020;

Kim et al., 2020; Woo et al., 2021, Yang et al., 2021; Kieseppä et al., 2022; Liu et al., 2022; Miola et al., 2022g; Olivito et al., 2022a, 2022b; Wei et al., 2022), or medical conditions (Brambilla et al., 2001; Yang et al., 2021, Ha et al., 2009, 2011; Gutiérrez-Galve et al., 2012; Maller et al., 2014, 2015; Cao et al., 2017; Squarcina et al., 2017; Janiri et al., 2019; Choi et al., 2020; Kim et al., 2020; Woo et al., 2021; Liu et al., 2022, Miola et al., 2022g; Olivito et al., 2022a, 2022b; Wei et al., 2022).

While Yang et al. 2021 specifically exclude patients with rapid cycling or with mixed features, other studies specified the euthymic condition as inclusion criteria (Hauser et al., 1999; Ha et al., 2011; Abè et al., 2018; Woo et al., 2021, Olivito et al., 2022b). Some studies reported that the presence of psychotic features (Caseras et al., 2015; Foley et al., 2018; Choi et al., 2020; Kim et al., 2020) or high suicidal risk (Choi et al., 2020; Kim et al., 2020) were ground for exclusion. The age range of participants (between 18 and 65) was specified by only a few studies (Ha et al., 2011; Woo et al., 2021; Miola et al., 2022g), and the same applies to left-handedness (Ha et al., 2009, 2011).

Obvious medical contraindications to MRI scanning – e.g., pregnancy – had to be excluded (Maller et al., 2014, 2015; Choi et al., 2020; Kim et al., 2020; Woo et al., 2021; Yang et al., 2021; Liu et al., 2022; Wei et al., 2022). Several studies also applied psychiatric comorbidity exclusion criteria (Brambilla et al., 2001; Lyoo et al., 2006; Gutiérrez-Galve et al., 2012; Maller et al., 2014, 2015; Squarcina et al., 2017; Choi et al., 2020; Kim et al., 2020; Woo et al., 2021; Olivito et al., 2022a, 2022b; Wei et al., 2022), with three of these studies indicating specifically the exclusion of DSM-IV-TR axis II disorders (Lyoo et al., 2006; Caseras et al., 2013, 2015). Some studies excluded any participants with intellectual disability (Janiri et al., 2019; Miola et al. 2022g; Olivito et al., 2022a, 2022b), and others considered lifetime alcohol/substance abuse as grounds for exclusion from the study (Hauser et al., 1999; Brambilla et al., 2001; Liu et al., 2010; Ha et al., 2011; Caseras et al., 2013, 2015; Foley et al., 2018; Janiri et al., 2019; Yang et al., 2021; Kieseppä et al., 2022; Miola et al., 2022g; Olivito et al., 2022a, 2022b).

5. Patient medication status in the included studies

Most of the patients were under pharmacologic treatment with mood stabilizers and/or antidepressants and/or antipsychotics and/or hypnotics at the time of the scans (Altshuler et al., 1995; Lyoo et al., 2006; Ha et al., 2009, 2011; Liu et al., 2010; Gutiérrez-Galve et al., 2012; Caseras et al., 2013, 2015; Maller et al., 2014, 2015; Abé et al., 2016; Squarcina et al., 2017; Cao et al., 2017; Abé et al., 2018; Foley et al., 2018; Janiri et al., 2019; Choi et al., 2020; Haukvik et al., 2020; Kim et al., 2020; Woo et al., 2021; Yang et al., 2021; Kieseppä et al., 2022; Liu et al., 2022; Mcwinney et al., 2022; Miola et al., 2022g; Olivito et al., 2022a, 2022b). Only one study included patients in treatment with lithium as monotherapy (Brambilla et al., 2001), while other studies did not specify the presence of medications (Hauser et al., 1999; Tighe et al., 2012; Haukvik et al., 2020) and one study reported among the exclusion criteria any medications that could affect the immune system or use of anti-inflammatory drugs (Wei et al., 2022).

3. Multivariate approaches and gap of knowledge

As previously reported, structural and functional MRI findings associated with BD subtypes and summarized in the previous chapter have not been consistently replicated. There are several reasons behind such inconsistencies. First, it is well known that BD is a very heterogeneous condition with different clinical sub-phenotypes (Coombes et al., 2020). Patients with BD differed in variables associated with the longitudinal course of their illness, including age at first symptoms and syndromal onset, duration of affective episodes, stage of illness, and cognitive impairment, which were not systematically reported and may represent noteworthy contributors to the observed heterogeneity within the BD population. Second, patients with BD commonly show co-occurring general medical disorders, including obesity, insulin resistance, and type 2 diabetes (Vancampfort et al., 2015; Miola et al., 2022c, 2023d), as well as co-occurring psychiatric conditions, including substance use disorders, anxiety, ADHD, and personality disorders (Krishnan et al., 2005; Hunt et al., 2016; Preti et al., 2016, 2018; Schiweck et al., 2021). Possible impact of such comorbidities was not systematically investigated in previous neuroimaging studies and can hinder the reliability of the results. Third, recruiting naïve patients with BD can be challenging, even during remission. Therefore, another important factor underlying the heterogeneity of the reported findings could include the treatment status, which varied significantly between the included MRI studies. For example, lithium exposure may increase gray matter volume, specifically in the limbic system, thalamus, and amygdala (Savitz et al., 2010; Hibar et al., 2016; Sani et al., 2018), whereas antipsychotic exposure has been associated with smaller brain volumes (Abramovic et al., 2016). Fourth, the cross-sectional design of most of the examined MRI studies limits the ability to make causal inferences and the generalizability of previous findings. Fifth, the limited sample size of some previous studies may result in insufficient statistical power to detect significant differences among BD subtypes when utilizing the specific metrics of interest. Sixth, from a methodological perspective, imaging-related settings

notably differed across the MRI investigations, including magnetic field strength, slice thickness, statistical methods, and data analysis.

Previous investigations have focused on individual whole brain or regional differences, mainly applying univariate approaches, including VBM, ROI, and tract-based spatial statistics to identify group differences in DTI values. However, the brain is organized in distinct networks which seem to better reflect the complex multivariate organization of the brain.

In this context, source-based morphometry (SBM), a multivariate and data-driven approach based on structural covariance, has been performed to detect structural network changes (Xu et al., 2009). SBM allows to investigate patterns of common variation among subjects (i.e., GM or WM patterns), using independent component analysis (ICA) to identify co-varying 'networks' and allows testing on covariation of these networks rather than investigating each voxel separately (Xu et al., 2009; Gupta et al., 2018). SBM offers several noteworthy advantages over VBM: (a) does not require a priori selection of regions to analyze; (b) permits the reduction of noise in results through the spatial filtration of artifactual sources (Xu et al., 2009) and has been suggested to be more sensitive in detecting GM atrophy than other methods such as VBM (Gupta et al., 2019); (c) takes into consideration the intricate interrelationship among voxels, allowing for a more comprehensive analysis; (d) allows computations based on mixing matrix parameters, which capture the covariation patterns of specific sources across individuals (Xu et al., 2009); (e) presents the advantage of reducing the number of comparisons required for analysis because the SBM approach is conducted on a small set of sources (Xu et al., 2009). Notably, SBM has already been used to study several neuropsychiatric disorders, including SCZ (Kaspàrek et al., 2010; Caprihan et al., 2011), BD (Lapomarda et al., 2021; Miola et al., 2022g), MDD (Wang et al., 2023), and BPD (Lapomarda et al., 2021).

Network analysis is another multivariate and data-driven approach which provides a graphic representation of the complex interrelationships involving behavioral variables that encompass psychopathological dimensions and cognitive domains (Galderisi et al., 2018; Galimberti et al.,

2020; Robinaugh et al., 2020; Karyakina et al., 2021). Networks consist of nodes, representing observed variables, and edges, representing their connections. Network centrality measures can be computed for each node in the network (Epskamp & Fried, 2018; Monteleone & Cascino, 2021): betweenness, which is the number of times that a node is involved in the shortest path between two other nodes (Brandes et al., 2001; Costantini et al., 2015); strength centrality, calculated as the sum of the edges connected to a node, each one weighted with its own thickness (Opsahl et al., 2010; Costantini et al., 2015), and closeness, which is the average distance from a node of interest to all other nodes in the network (Freeman et al., 1979; Costantini et al., 2015). Network analysis methods have recently found applications in integrating behavioral variables encompassing traits, symptoms, cognitive performance, and associated structural and functional neural correlates within unified networks. This approach has been particularly valuable in exploring the connections between these elements in psychiatric and neurodevelopmental conditions, including but not limited to depression (Hilland et al., 2020) and autism (Bathelt et al., 2022). This method has shown several advantages over traditional approaches. Analyzing both brain and behavioral data within the same analytical paradigm offers easier visualization and simultaneous estimation of the complex pattern of relationships between behavioral and structural properties of the brain (Simpson-Kent et al., 2021; Miola et al., 2023f).

As previously underscored, neural correlates differentiating the main BD subtypes remain controversial, and debates persist regarding the optimal approach to manage the heterogeneity behind the broad concept of manic-depressive illness. Distinguishing between BD subtypes poses a significant challenge that extends beyond mere nosological considerations, given its profound implications for disease management and prognosis (Tondo et al., 2022b; Miola et al., 2023f).

In this context, the exploration of structural brain networks, which are believed to offer a more comprehensive representation of the intricate multivariate organization of the brain, coupled with an in-depth examination of the interplay between network covariance patterns, clinical variables, and psychological functioning, have not been systematically investigated across the BD subtypes.

Conducting such in-depth analyses may help to refine the pathophysiology underlying the major BD subtypes, help to address the long-standing challenge of delayed diagnosis of BD, and allow for more accurate prognostic prediction and personalized interventions for these clinical populations.

In addition, although the clinical relevance of impaired affective cognition in BD (Miskowiak et al., 2019), the relationship between BD and emotional processing and the neurobiological bases underlying these conditions are still poorly understood. In this context, the ISBD Targeting Cognition Task Force recommends FER among the domains for future research (Miskowiak et al., 2019). Additionally, FER performance seems to be a promising tool to better discriminate different psychiatric populations (De Prisco et al., 2023). Although a few evidence underscored that patients with BD, even when euthymic, show trait-associated FER impairment (Rocca et al., 2009), critical aspects still require clarification. These include elucidating the neuroanatomical basis of general and selective FER impairments in euthymic patients with BD, the clinical relevance of FER processing to morbidity and daily functioning, and the differences between BD subtypes (Miola et al., 2023f).

On the other hand, affective temperaments represent subclinical manifestations and, acting as a bridge between genes and clinical manifestations, could represent vulnerability factors and precursors of BD (Akiskal and Akiskal, 2005; Evans et al., 2005; Rihmer et al., 2010; Fountoulakis et al., 2016). Furthermore, affective temperaments seem to have a crucial role in the long-term course and the prognosis of BD (Miola et al., 2021). In this context, preliminary evidence found that affective temperaments are associated with white matter integrity in healthy unaffected relatives of patients with BD (Sprooten et al., 2011) and in a group of mixed patients with major affective disorders (Serafini et al., 2011). However, the relationship between affective temperament ratings and white matter integrity using FA, a sensitive index commonly used to measure microscopic white matter integrity (Wijtenburg et al., 2013), has not been systematically investigated between the main BD subtypes.

The existing knowledge gap prompted the following studies, in which we adopted an integrated approach encompassing the analysis of clinical, behavioral, and neuroimaging data, leveraging multivariate approaches to provide a comprehensive investigation of the main BD subtypes.

4. Research studies

4.1 Gray matter volume covariance networks are associated with altered emotional processing in bipolar disorder: a source-based morphometry study

Aims

The current study aimed to investigate differences in structural network covariance between distinct BD subtypes when compared to HC, matched for age, sex, handedness, and IQ, using an SBM approach. Furthermore, this work proposed to explore the potential links between these structural alterations and both hot (emotional processing) and cold (executive functions) cognition across BD-I, BD-II, and HC.

We hypothesized that patients with BD would exhibit a reduction in structural network covariance, with the magnitude of this effect being the greatest in those with BD-I.

Methods

Study participants

Fifty-four patients with BD (24 BD-I, 30 BD-II) and 45 HC matched with age, sex, handedness, and IQ were recruited in this study. Written informed consent was obtained from all participants after a complete explanation of the study. The local Ethics Committee authorized this study, and the Helsinki Declaration of 1975 guidelines were followed.

Patients were diagnosed with BD using the Structured Clinical Interview for DSM-5-Patient Edition and had stable drug treatment (≥ 1 month). Exclusion criteria for all participants were (a) age <18 or >65 years, (b) history of alcohol or drug abuse in the previous six months, (c) lifetime drug dependence, (d) traumatic head injury with loss of consciousness, (e) past or present major medical illness, including neurological disorders, and (f) mental retardation. In addition, history or current diagnosis of psychiatric disorders or drug treatment were exclusion criteria for HC.

Clinical measures and neuropsychology

Affective symptoms were evaluated using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959), and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and daily functioning was quantified using the Global Assessment of Functioning (GAF). A detailed history of mood disorders was recorded, including illness duration, age of illness onset, familiarity for BD, the number of lifetime affective episodes, and past occurrence of psychotic symptoms. Current drug treatments were measured using the defined daily dose (DDD) (Nosè & Barbui, 2008), and serum lithium levels and their duration were also collected.

For the neuropsychological measures, the Tower of Hanoi (TOH) to investigate executive functions and the Facial Emotion Recognition (FER) task for emotional processing were administered to patients and HC using PEBL software (http://pebl.sourceforge.net/).

Image Acquisition and Imaging Processing

High-resolution structural data were acquired using a 3T MR-scanner (3 Tesla Philips Ingenia, Best, The Netherlands) with a 32-channel quadrature head coil. Participants with BD and HC underwent whole-brain 3D-T1 magnetization-prepared rapid gradient-echo sequence in the sagittal plane with the following parameters: TR/TE= 6676ms/3ms, FOV= 240mm; flip-angle= 8°, resolution= 1.0×1.0×1.0mm3; number of slices=181. Any brain abnormalities, such as infarcts, hemorrhages, or tumors, were excluded after an expert neuroradiologist (RM) evaluation.

Data were preprocessed using the Computational Anatomy Toolbox for SPM (CAT12). Spatially normalized and segmented images were modulated and smoothed using an 8-mm full-width half-maximum Gaussian kernel. First, a voxel-wise general linear model (GLM) with total intracranial volume (TIV) and age as covariates was used to compare gray matter volume (GMV)

across BD groups and HC using pairwise univariate linear contrasts. Nonparametric testing was employed using the threshold-free cluster enhancement method, involving 5000 permutations for statistical analysis. Family-wise correction at the cluster-level was conducted with a significance threshold of $\alpha = 0.05$.

Source-based morphometry (SBM)

Comprehensive methodological details regarding SBM analysis are available elsewhere (Xu et al., 2009). In summary, we conducted a spatial independent component analysis (ICA) on preprocessed GMV images of all subjects using the Infomax algorithm, implemented through the "Group ICA for fMRI Toolbox" (GIFT; available at https://trendscenter.org/software/gift/). The determination of the number of components was based on the 'minimum description length' criteria. All GMV images were arrayed into one 99-row subject-by-image matrix, that was then decomposed into a source matrix, indicating the relationship between components and brain voxels, and one mixing matrix, which represents the relationship between components and study participants. To ensure the reliability of our analysis, we performed 50 bootstrapped and permuted ICA estimations using the ICASSO algorithm. Components with a coefficient of stability exceeding 0.8 were included for subsequent analysis. We retained components that exhibited spatial correlations ($r > 0.1$, $p < 0.001$) with clusters showing GMV changes in patients with BD for further group analyses.

In our group analyses, we initially calculated component-related differences in GMV between BD-I, BD-II, and HC groups. These comparisons were carried out using ANCOVAs, with age and TIV serving as covariates in the columns of the mixing matrices associated with the selected components. Tukey's post hoc test ($p < 0.05$) was applied to identify specific group differences. Maps displaying components with significant group differences were then overlaid onto a normalized Montreal Neurological Institute (MNI) anatomical template. Additionally, we conducted supplementary analyses by incorporating sex as a covariate and by limiting the sample

to euthymic patients at the time of the scan, with the aim of mitigating potential confounding effects, if any.

Statistical analyses

We compared diagnostic groups using $\chi 2$-tests for categorical data and one-way-ANOVA for continuous variables, with pairwise chi-square/Tukey post-hoc comparisons in case of statistical significance. To explore the relationships between structural changes, clinical data, and cold and hot cognition measures, we employed Pearson's or Spearman's correlation, consistently based on data distribution. The significance threshold was set at $p < 0.05$.

Results

Study participants

Patients with BD did not significantly differ from HC in terms of age, sex, handedness, and IQ scores (all p's > 0.10). Patients with BD-I were more likely to present a significantly greater occurrence of past psychotic symptoms ($p < 0.001$) and exhibited lower GAF scores ($p = 0.003$). Again, compared with those with BD-II, patients with BD-I had lower use of antidepressants ($p = 0.001$), greater use of antipsychotics ($p = 0.033$), and a trend for increased lifetime lithium exposure ($p = 0.084$). BD subtypes did not significantly differ concerning the illness duration, affective symptoms, proportion of patients in the euthymic state, and plasma levels of lithium (all p's > 0.10). Detailed demographic and clinical data are summarized in Table 1.

TABLE 1. Sociodemographic and clinical characteristics of BD-I, BD-II, and HC.

Characteristics	BD-I (N=24)	BD-II (N=30)	HC (N=45)	F or χ	df	P
Age (years), mean ± SD	43.2 ± 13.7	39.5 ± 12.4	41.5 ± 13.1	0.619	2	0.54
Males, n (%)	18 (75)	19 (63.33)	25 (55.55)	2.54	2	0.281
IQ, mean ± SD	103 ± 13	108 ± 9.46	110 ± 9.05	2.00	2	0.151
Duration of illness (years), mean ± SD	17.8 ± 11.4	12.8 ± 10.5		2.67	1	0.109
Childhood-onset, n (%)	7 (29.16)	11 (36.66)		0.338	1	0.561

Current mood state:						
Euthymia, n (%)	18 (75)	28 (93.3)		1.48	1	0.224
Depression, n (%)	2 (8.3)	2 (6.7)		0.054	1	0.816
Hypomania, n (%)	2 (8.3)	0		2.60	1	0.107
Mania/mixed n (%)	2 (8.3)	0		2.60	1	0.107
Previous psychotic symptoms	17 (70.8)	1 (3.3)		27.3	1	<0.001
Familiarity for BD n (%)	16 (66.7)	19 (63.3)		0.0650	1	0.799
Number of past episodes:						
Depressive						
No episodes	8	1				
Single episode	0	2				
Recurrent episodes	13	20				
Manic						
No episodes	1	21				
Single episode	9	0				
Recurrent episodes	11	0				
Mixed						
No episodes	14	21				
Single episode	5	1				
Recurrent episodes	2	0				
Time since last episode (months), mean ± SD	39.8 ± 65.1	11.1 ± 7.47		4.81	1	0.034
HAMD, mean ± SD	3.9 ± 8.99	1.63 ± 2.22		1.45	1	0.236
HAMA, mean ± SD	3.9 ± 8.01	1.38 ± 1.88		2.26	1	0.140
MADRS, mean ± SD	5.0 ± 11.8	2.08 ± 4.17		1.28	1	0.264
YMRS, mean ± SD	4.57 ± 11.2	1.04 ± 2.40		2.25	1	0.141
PANSS, mean ± SD	2.95 ± 8.36	0				
GAF, mean ± SD	61.7 ± 26.6	79.1 ± 10.1		10.2	1	0.003
Past pharmacotherapy						
Antidepressants, n (%)	10 (41.7)	13 (43.3)		0.015	1	0.902
Antipsychotics, n (%)	15 (62.5)	11 (36.7)		3.56	1	0.059
Antiepileptics, n (%)	7 (29.2)	4 (13.3)		2.06	1	0.151
Benzodiazepines, n (%)	13 (54.2)	15 (50)		0.093	1	0.761
Current pharmacotheraphy						
Antidepressants, n (%)	7 (29.2)	22 (73.3)		10.5	1	0.001
Antipsychotics, n (%)	15 (62.5)	10 (33.3)		4.56	1	0.033
Antiepileptics, n (%)	6 (25)	4 (13.3)		1.20	1	0.273
Lithium, n (%)	24 (100)	30 (100)				
Lithium treatment duration (months), mean ± SD	60.2 ± 87.9	27.4 ± 40.1		3.11	1	0.084
Lithium plasma level (mmol/L), mean ± SD	0.574 ± 0.191	0.521 ± 0.170		1.09	1	0.301

Legend. IQ, intelligence quotient; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; MADRS, Montgomery and Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; SD, standard deviation; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

Neuropsychology measures

A main effect of group ($p = 0.032$) on the completion time at the TOH emerged, with BD-I displaying a significantly longer time to complete the task relative to HC ($p = 0.032$). Conversely, no significant differences were found between HC and patients with BD-II ($p = 0.218$) nor between patient subgroups ($p = 0.532$).

Regarding emotional processing measures, a main effect of group on the reaction time ($p = 0.004$) and the rate-corrected accuracy at the FER task emerged, with BD-I showing longer reaction time and lower rate-corrected accuracy (Vandierendonck, 2017) relative to BD-II ($p = 0.029$, $p = 0.017$) and HC ($p = 0.042$, $p = 0.017$). On the contrary, no significant differences between patients with BD-II and HC emerged ($p > 0.2$) (Table 2).

TABLE 2. Neuropsychological test performance of the samples.

	BD-I	**BD-II**	**HC**	**F**	**p**
TOH, completion time (msec), mean ± SD	5143 ± 2086	4498 ± 2265	3683 ± 1631	3.64	0.032
FER, rate-corrected accuracy (a.u.), mean ± SD	0.023 ± 0.007	0.031 ±0.009	0.031 ± 0.010	6.440	0.004
FER, mean time (msec), mean ± SD	3780 ± 1666	2895 ± 910	2989 ± 819	3.799	0.027

Legend. TOH, Tower of Hanoi; FER, Facial emotion recognition task; SD, standard deviation; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls; a.u., arbitrary units.

Voxel-based morphometry (VBM) and Source-based morphometry (SBM)

Patients with BD-I exhibited seven clusters of significant GMV reduction located bilaterally in the superior, middle, and inferior temporal gyri, in the right middle and inferior occipital gyrus, right insula, left inferior parietal lobule, and culmen relative to HC. Conversely, there were no significant GMV differences between BD-II and patient subgroups. The VBM results are summarized in Figure 1.

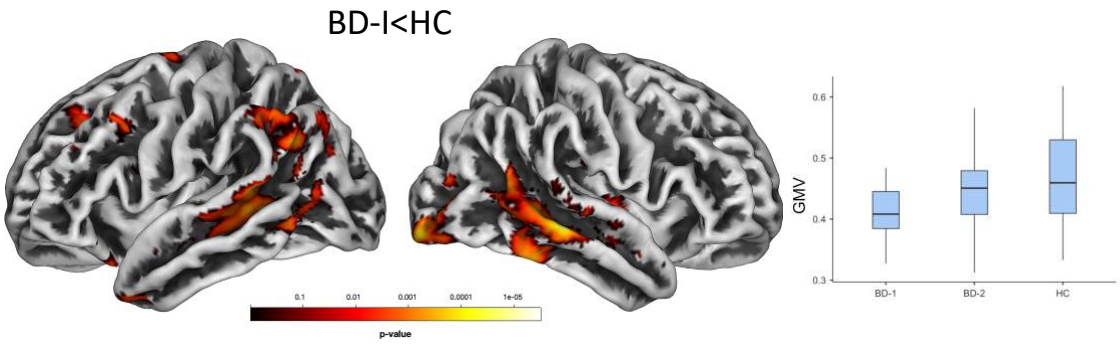

Figure 1. Spatial maps showing gray matter volume loss in patients with BD-I relative to HC. Maps of left and right hemisphere, respectively, are displayed on a Montreal Neurological Institute template with a threshold of voxel-wise p<0.005 uncorrected for display purposes. The color bar represents p values. BD-I, bipolar disorder type I; HC, healthy controls.

For the SBM results, twenty components were computed. IC19 was correlated with GMV changes (r = 0.2) and spanned across the superior, middle, and inferior temporal gyri, middle and inferior occipital regions, inferior parietal lobe, precuneus, fusiform gyrus, inferior frontal gyrus, and anterior cingulate cortex (Figure 2). IC13 was correlated with VBM changes (r = 0.15) and encompassed predominantly the temporal, cingulate, precuneus, and insular cortex. Of note, a significant effect of diagnosis ($F(2,96) = 4.21$, $p = 0.018$) in the IC19 loadings was found, with planned comparisons showing significant differences only between patients with BD-I and HC ($p = 0.028$). Moreover, IC13 loadings also displayed a significant effect of diagnosis ($F(2,96) = 3.33$, $p = 0.040$), with planned comparisons revealing only a trend for significance for the comparison between patients with BD-I and HC ($p = 0.067$). These findings were consistently replicated when incorporating sex as a covariate and when focusing on the subgroup of individuals who were euthymic at the time of the scan.

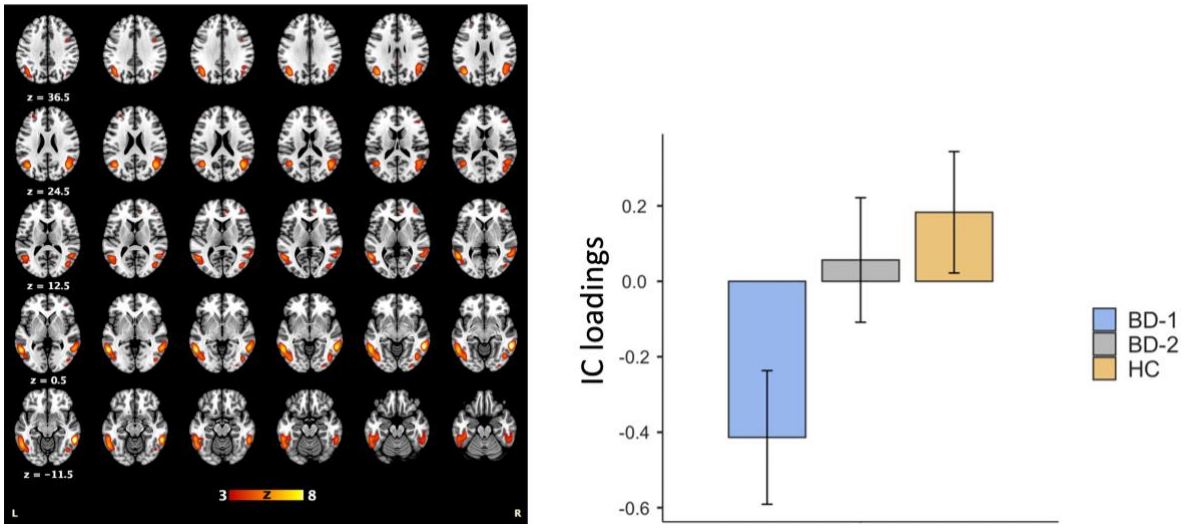

Figure 2. SBM component (IC19) entailing a prefrontal-temporal-occipital network showed significantly lower gray mater volume covariance in patients with BD-I compared to HC, but not to the other groups. Transversal 2-mm slices are rendered on a Montreal Neurological Institute template. L and R indicate the left and right brain hemispheres, respectively. Axial planes, z, are indicated on the first column. The color bar indicates Z-scores. Y-axis represents IC loadings for the SBM component, quantified in arbitrary units (a.u.). BD-I, bipolar disorder type I; HC, healthy controls.

Brain-behavior relationships

A negative correlation between the number of previous manic episodes and the GMV loss in the right superior, middle, and inferior temporal gyri (rho = -0.463, p = 0.026), as well as with the IC19 loadings emerged (rho = -0456, p = 0.029). In patients with BD-I, FER response time was negatively correlated with GMV in the inferior occipital gyrus (r = -0.557, p = 0.039) and in the superior temporal gyrus (r = -0.545, p = 0.044). In patients with BD-I, the completion time of TOH was negatively correlated with IC19 loadings (rho = -0.510, p = 0.039). However, none of the exploratory correlations involving GMV and IC loadings with other cognitive and clinical variables reached statistical significance. Figure 3 reports scatter plots of GM and cognition performance in patients with BD-I.

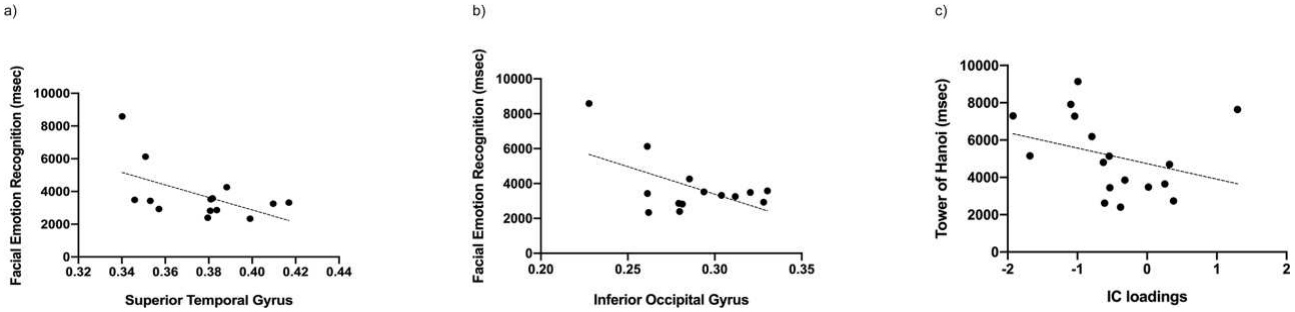

Figure 3. Scatterplots of gray matter volume (GMV), facial emotion recognition (FER), and cognition performance in patients with BD-I. The average reaction time at the FER task was negatively correlated with GMV in two distinct brain regions: (a) superior temporal gyrus and (b) inferior occipital gyrus. The average reaction time at the TOH was negatively correlated with the IC19 loadings (c). BD-I, bipolar disorder type I.

4.2 Network dysfunction of sadness facial expression processing and morphometry in euthymic bipolar disorder

Aims

In the first study, we found that patients with BD-I displayed a general deficit in FER and correlated with a loss of GMV in the temporal-occipital regions in BD-I.

The second study aimed to (a) investigate FER performance, with a particular interest in sadness-related FER, in BD phenotypes compared to HCs; (b) to explore the correlation between FER performance, morbidity indices, and daily functioning in such populations; (c) to test the association between cortico-limbic regions implicated in emotional processing and FER performance through a network analysis.

We hypothesized that euthymic patients with BD-I could exhibit deficits in emotional processing, particularly in relation to recognizing sadness. We also posited that impaired FER performance could be linked to a reduced interrelationship between the brain regions implicated in emotional processing and recognition. Lastly, we hypothesized that such impairments might be correlated with clinical outcomes and overall functioning in individuals with BD-I.

Methods

Study population

A sample of 48 patients with BD (20 BD-I and 28 BD-II) and 45 HC were enrolled from the psychiatric ward and the outpatient service of the Padua University Hospital. Inclusion and exclusion criteria were the same as reported in the first study.

Clinical assessment and FER task

We used the same rating scales as those employed in the first study for clinical assessment. A detailed history of mood disorders and past and current pharmacological treatments were also recorded.

The FER task was used to investigate emotional processing and was administered utilizing PEBL software (http://pebl.sourceforge.net/) (De Panfilis et al., 2019). The FER task consisted of 140 emotion-expressing faces, with four types of expressions [disgust (n=40), anger (n=40), sadness (n=40), and neutral (n=20)] being presented in pseudo-randomized order. Accuracy and reaction time were extracted, and the FER performance was expressed as the ratio between the percent accuracy and the mean reaction time for all (FER-total) and individual emotions (Vandierendock, 2017). Due to the robust a priori hypotheses concerning impaired processing of sadness in BD (De Prisco et al., 2023), our analysis focused exclusively on sadness-related FER performance and FER-neutral as a control variable.

Voxel-Based Morphometry (VBM)

As in the first study, structural MRI data were preprocessed using the Computational Anatomy Toolbox for SPM (CAT12) (http:// www.neuro.uni-jena.de/cat/), a toolbox running within the Statistical Parametric Mapping analysis package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). After data preprocessing, modulated normalized GMV and white matter volumes were smoothed using an 8-mm Full-Width Half Maximum (FWHM) Gaussian kernel, and a 0.2 absolute masking threshold was applied.

TIV was calculated to account for variations in brain size. The GMV of each of the nine bilateral ROIs selected from the n30r83 Hammersmith atlas (http://brain-development.org/brain-atlases/adult-brain-maximum-probability-map-hammers-mith-atlas-n30r83-in-mni-space/) was computed and averaged between the two hemispheres. In line with our strong a priori hypothesis, we focused on brain regions implicated in FER performance. These regions, identified in previous literature, encompass the amygdala, anterior cingulate cortex, orbitofrontal cortex, fusiform gyrus, superior frontal gyrus, medial frontal gyrus, inferior frontal gyrus, hippocampus, and insula.

Statistical analysis

For analyzing socio-demographic and clinical data among diagnostic groups, one-way ANOVA for continuous data and $\chi 2$-tests for categorical variables were used, with pairwise $\chi 2$/Tukey post-hoc comparisons in case of statistical significance. The FER-total, as well as the FER-sadness, and the FER-neutral scores were compared among BD-I, BD-II, and HC groups with ANOVA and repeated-measures-ANOVA with planned-pairwise comparisons (FER-sadness vs. FER-neutral for each group), using the Bonferroni correction for the number of comparisons ($p=0.05/6=0.008$, 3 between-group comparisons x 2 emotions=6), respectively. A voxel-wise GLM with age and TIV as covariates was employed to compare GMV among the three diagnoses using pairwise post hoc t-tests. Clinical variables were correlated with FER scores and sadness-related FER performance using Pearson's and Spearman's correlation based on data distribution for each group. A false discovery rate correction for multiple comparisons was used for ROI comparisons across diagnoses. Statistical analysis was conducted using R (http://www.rstudio.com/) and JAMOVI (Version 1.2) (https://www.jamovi.org). The significance threshold for all tests was defined as $p<0.05$.

Network analysis

The relationship between the FER-sadness and regional GMV was analyzed using network analysis. A network analysis was computed for each group with 11 nodes: 9 GMV ROIs implicated in FER processing and 2 FER scores (FER-sadness and FER-neutral as a control variable). Partial correlations between variables, obtained after partialling out all the other variables, were represented by the 'edges' connecting the nodes. Three 'centrality measures' (betweenness, closeness, and strength centrality) were also computed for each node. A Graphical Gaussian Model of the data was fit using the EBICglasso estimator. We ensured the stability of our findings through a bootstrapping procedure, which generated 95% confidence intervals for each edge and calculated the average edge value based on 5,000 resamplings. To compare

network structures and centrality measures between diagnostic groups, we employed the Network Comparison Test (NCT), a two-tailed permutation test on pairwise differences with 5000 resamplings (Van Borkulo et al., 2022). We compared differences in network structures using three invariance measures: network structure invariance, global strength invariance, and edge invariance. Network analyses were performed using JASP version 0.14.1 (JASP team 2020), while the NCT was performed using R (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL https://www.rstudio.com/.) For all analyses, the significance level was set at $p < 0.05$.

Results

Study population

Patients with BD-I, BD-II, and HC did not significantly differ in age, sex, and handedness (all p's>0.1). When compared to patients with BD-II, those with BD-I showed a significantly higher occurrence of past psychotic symptoms ($p<0.001$), lower GAF scores ($p=0.004$), and a lower number of past depressive and hypomanic episodes ($p=0.033$ and $p=0.004$, respectively). Furthermore, patients with BD-II were more likely to be treated with antidepressants ($p<0.001$) and less likely to use antipsychotics ($p=0.007$) compared with patients with BD-I. No significant differences were observed between the patient groups in terms of illness duration, scores on the HAM-D, HAM-A, MADRS, and YMRS, as well as family history of BD, use of anticonvulsant and lithium medications, or current plasma lithium levels (all p-values > 0.1). Additionally, no psychiatric comorbidities were identified in the enrolled patients with BD-I and BD-II. A summary of the sociodemographic and clinical characteristics of the study samples can be found in Table 3.

Table 3. Sociodemographic and clinical characteristics of the study participants

Characteristics	BD-I (N=20)	BD-II (N=28)	HC (N=45)	F or χ^2	P
Age (years), mean ± SD	45.5 ± 12.6	38.9 ± 12.6	40.1 ± 12.8	1.745	0.186
Males, n (%)	13 (65)	19 (67.86)	23 (58.97)	0.589	0.745
Duration of illness (years), mean ± SD	16.6 ± 10.1	12.8 ± 10.7		1.239	0.222
Childhood-onset, n (%)	3 (15.0)	11 (39.29)		-1.852	0.070
Previous psychotic symptoms, n (%)	11 (55.0)	10 (36.0)		4.899	<0.001
Familiarity for BD, n (%)	15 (75.0)	18 (64.29)		0.778	0.441
Number of past episodes					
Depressive (N= 0/1/2+)	6/0/12	1/2/19		6.820	0.033
Manic (N= 0/1/2+)	2/8/8	20/0/0		30.707	<0.001
Hypomanic (N= 0/1/2+)	11/3/4	2/6/12		11.156	0.004
Mixed (N= 0/1/2+)	14/4/0	20/0/0		5.200	0.023
HAMD, mean ± SD	2.83 ± 5.52	1.69 ± 2.25		0.900	0.374
HAMA, mean ± SD	3.33 ± 6.21	1.45 ± 1.90		1.389	0.173
MADRS, mean ± SD	3.67 ± 7.23	2.17 ± 4.24		0.827	0.413
YMRS, mean ± SD	3.00 ± 6.70	1.09 ± 2.44		1.248	0.220
GAF, mean ± SD	65.00 ± 23.37	80.58 ± 8.41		-3.076	0.004
Current pharmacotherapy					
Antidepressants, n (%)	6 (30.0)	22 (78.6)		-3.365	<0.001
Antipsychotics, n (%)	15 (75.0)	10 (35.7)		2.686	0.007
Anticonvulsants, n (%)	6 (30.0)	4 (14.3)		1.322	0.187
Lithium, n (%)	19 (95.0)	28 (100)		-1.196	0.230
Lithium treatment duration (months), mean ± SD	89.54 ± 118.86	28.25 ± 40.60		2.531	0.015
Lithium plasma level (mmol/L), mean ± SD	0.550 ± 0.270	0.522 ± 0.170		0.427	0.672

Legend. HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning; SD, standard deviation; Current pharmacotherapy, 0 = 0, 1 ≤ 2, 2 ≥ 3. BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

ROI-based VBM analysis

No significant differences were observed in the average GMV of each ROI across BD-I, BD-II, and HC, as summarized in Table 4.

Table 4. Brain morphometry of the regions implicated in facial emotion recognition (FER) for each diagnostic group.

		Gray matter volume (M± SD, µl)				
Region of interest	**Atlas labels**	**BD-I**	**BD-II**	**HC**	**F**	**p**
Hippocampus	Hip	2.102 ± 0.115	2.129 ± 0.153	2.128 ± 0.205	0.057	0.944
Amygdala	Amy	1.755 ± 0.132	1.824 ± 0.142	1.797 ± 0.175	0.194	0.823
Fusiform Gyrus	FusGy	3.049 ± 0.309	3.223 ± 0.380	3.240 ± 0.314	1.543	0.219
Insula	Ins	7.504 ± 0.548	7.926 ± 0.737	7.852 ± 0.829	0.352	0.704
Anterior Cingulate Cortex	AntCingGy	4.110 ± 0.375	4.146 ± 0.553	4.193 ± 0.469	0.332	0.718
Middle Frontal Gyrus	MidFrontGy	19.605 ± 2.075	20.214 ± 2.361	20.342 ± 2.176	0.243	0.784
Orbitofrontal Gyrus	OrbFrontGy	11.824 ± 1.014	12.621 ± 1.226	12.422 ± 1.189	0.984	0.3782
Inferior Frontal Gyrus	InfFrontGy	9.131 ± 0.770	9.701 ± 0.998	9.462 ± 1.001	0.482	0.619
Superior Frontal Gyrus	SupFrontGy	29.367 ± 2.836	30.735 ± 2.993	30.770 ± 3.589	0.386	0.680

Legend. Gray matter volume (mean± standard devation, µl) calculated using voxel-based morphometric analysis is reported for each ROI drawn from the atlas labels of the n30r83 Hammersmith atlas. P-values are false discovery rate-corrected for multiple comparisons. BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

FER Task

An effect of diagnosis on FER-total scores [$F(2,90)=8.928$, $p<0.001$] emerged, with patients with BD-I showing significantly worse performance when compared to those with BD-II and HC ($p<0.001$). Conversely, no significant differences between patients with BD-II and HC were found ($p=0.9$). In patients with BD-I, FER-total scores were negatively correlated with the duration of illness ($r=-0.543$, $p=0.02$) and positively correlated with the GAF scores ($r=0.656$, $p=0.015$). Performing the emotion-by-diagnosis ANOVA, the effect of diagnosis ($p<0.001$) has been confirmed. Specifically, patients with BD-I had the poorest performance relative to those with BD-II and HC (all p's<0.001). The same analysis confirmed the effect of emotion [$F(1,84)=31.02$, $p<0.001$] with the poorest performance for sadness relative to neutral [$t(84)=5.57$, $p<0.001$], and a marginal significance for their interaction [$F(2,84)=2.68$, $p=0.07$]. Again, planned comparisons with Bonferroni-corrected significance revealed significant differences for FER-sadness vs. FER-neutral in patients with BD-I [$F(2,84)= 4.081$, $p<0.001$] when compared with HC [$F(2,84)= 4.226$, $p<0.001$] but not with patients with BD-II [$F(2,84)= 1.433$, $p=0.156$] (see Figure 4).

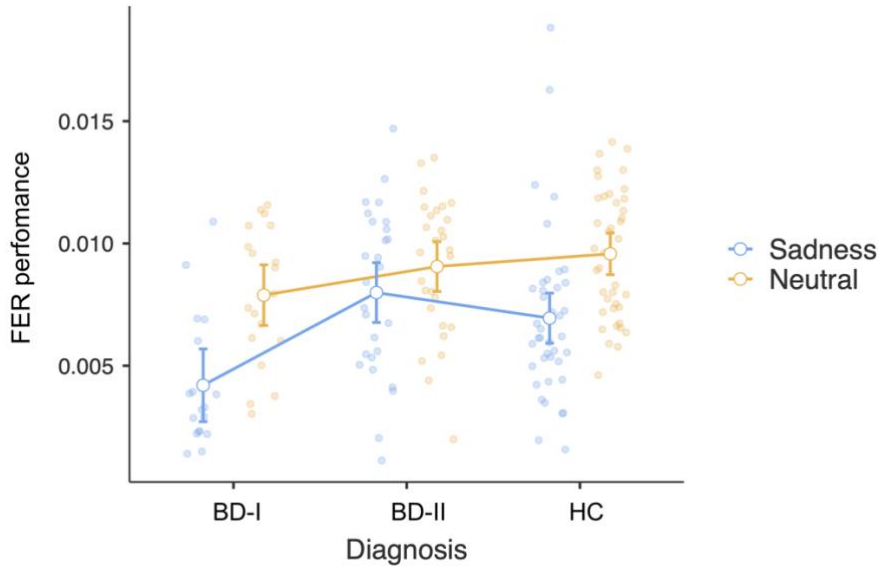

Figure 4. Sadness-related FER performance (FER-sadness) is altered in patients with BD-I relative to those with BD-II and HC. BD-I and HC show reduced FER performance during the presentation of sadness (FER-sadness) compared to neutral in contrast with BD-II, who exhibit similar performance independent of the facial emotion. The colored dots represent FER performance for each group and emotion (neutral in blue, and sadness in yellow); the white dots indicate the mean, and the bars the 95% confidence intervals for each emotion and diagnosis. FER performance scores are computed as the ratio between the % accuracy and the mean reaction time. FER, facial emotion recognition task; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

In patients with BD-I, sadness-related FER performance was negatively correlated with the illness duration (r=-0.576, p=0.012) and with the number of previous manic episodes (r=-0.545, p=0.024), and positively correlated with the GAF score (r=0.569, p=0.043) (Figure 5).

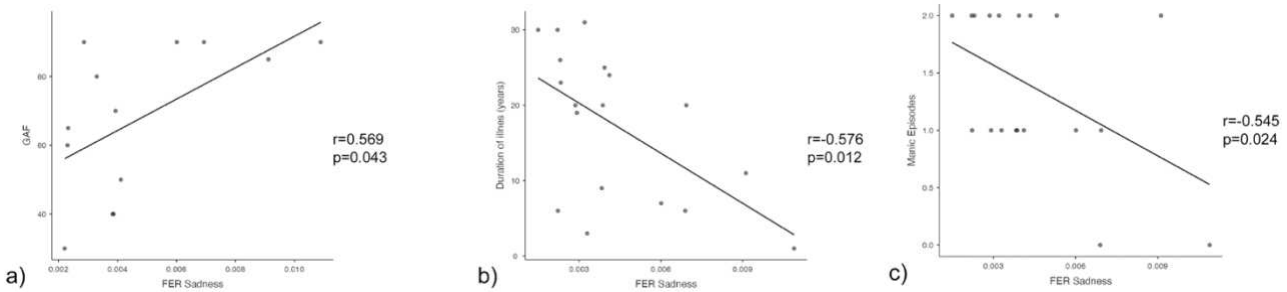

Figure 5. Sadness-related FER performance (FER-sadness) correlates with clinical features and daily functioning in patients with BD-I. Scatterplots indicate the relationship between FER-sadness scores, calculated as %accuracy/mean reaction time, and (a) the Global Assessment of Functioning (GAF) scale scores, (b) duration of illness, (c) the number of previous manic episodes. Spearman's r and p-value are reported on the right-hand side of each scatter plot. FER, facial emotion recognition task; BD-I, bipolar disorder type I.

In patients with BD-I, FER-total, and FER scores for each emotion did not correlate with the antidepressant dose nor with plasma lithium levels (all p's > 0.05). Conversely, in patients with BD-I, FER-total, and FER-sadness scores were significantly correlated with antipsychotic dose (rho=-0.561, p=0.02, and rho=-0.508, p=0.04, respectively). No significant correlations emerged between FER scores and clinical variables in patients with BD-II.

Network analysis

The network plot of patients with BD-I revealed a reduced interrelationship in the frontal-insular-occipital regions when compared to those with BD-II and HC, as well as between FER-sadness and FER-neutral (Figure 6). In patients with BD-I, FER-sadness, and FER-neutral were not associated with frontal-insular-occipital regions, with the strength of the edge between FER-sadness and the amygdala being notably greater in BD-I compared with the other groups (HC exhibited a negative sign in this edge).

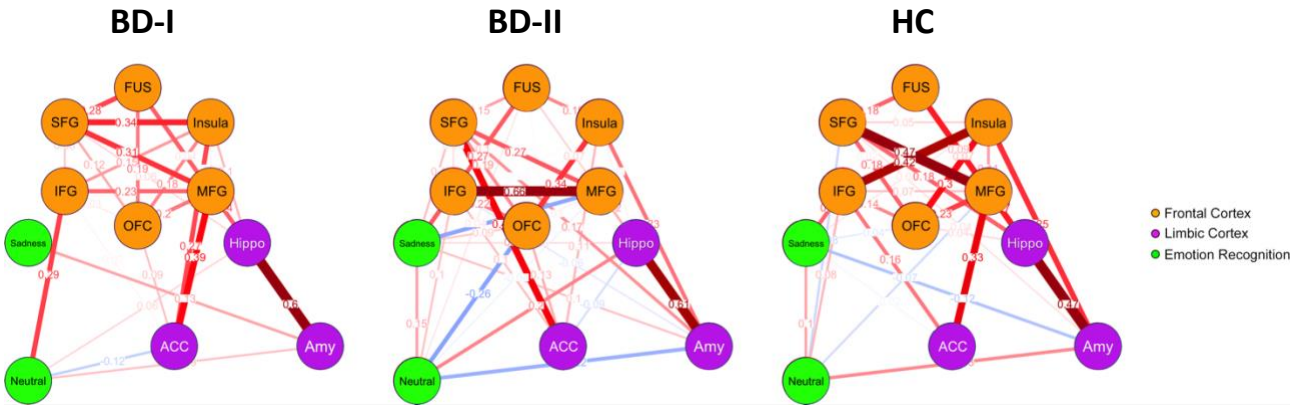

Figure 6. Network plot of the relationship between FER and brain morphometry of the regions implicated in emotional processing for each diagnostic group. The thickness of the edge indicates the

strength of the correlation, and its color indicates the sign of the correlation. Blue lines represent negative associations; red lines represent positive associations. Nodes are organized by color: green indicates emotion recognition (Sadness= FER-sadness score, Neutral= FER- neutral score); purple indicates limbic cortex morphometry (Insula, Amy= Amygdala, Hippo= Hippocampus, ACC= Anterior Cingulate); orange indicates fronto-insulo-temporal cortex morphometry (FUS= Fusiform Gyrus, SFG= Superior Frontal Gyrus, MFG= Medial Frontal Gyrus, IFG= Inferior Frontal Gyrus). FER, facial emotion recognition task; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

NCT confirmed a significant difference in the network structure invariance between patients with BD-I and HC ($p<0.001$) as well as between patients with BD-II and HC ($p<0.001$). Conversely, there were no significant differences between the BD subtypes ($p=0.85$). No significant differences in terms of global strength invariance were found among groups (all p's >0.1). Lastly, the edge invariance test, which compares the edge strength, revealed a stronger positive relationship between amygdala GMV and FER-sadness in patients with BD-I relative to HC ($p=0.005$), whereas no significant differences emerged between HC and those with BD-II nor between BD subtypes (all p's>0.1). Lastly, no significant differences in terms of centrality measures were found between diagnoses (Table 5).

Table 5. Centrality measures per node across BD-I, BD-II, and HC.

	BD-I			BD-II			HC		
Node	**Betweenness**	**Closeness**	**Strength**	**Betweenness**	**Closeness**	**Strength**	**Betweenness**	**Closeness**	**Strength**
Sadness	-0.899	-2.233	-2.343	-0.294	-0.867	-0.784	-1.033	-1.442	-1.171
Neutral	-0.428	-0.868	-0.943	-0.587	-0.668	-0.043	-1.033	-1.900	-1.276
Hippocampus	-0.899	-0.448	0.071	-1.174	-0.909	-0.052	-0.323	0.594	-0.388
Amygdala	1.455	0.012	0.738	0.000	-0.129	1.438	2.044	1.215	1.147
Fusiform gyrus	1.141	0.814	-0.313	-0.881	-1.072	-1.458	-1.033	-0.123	-0.781
Insula	-0.742	0.812	0.733	0.000	0.749	-0.509	1.334	1.322	0.787
Anterior Cingulate cortex	-0.899	0.061	0.155	-1.174	-1.074	-1.535	-0.559	-0.668	-1.150
Middle Frontal gyrus	1.141	1.010	1.047	1.468	0.880	1.004	0.151	0.193	1.423
Orbito-Frontal gyrus	-0.899	0.148	-0.084	0.881	1.023	0.328	-0.323	0.210	0.096
Inferior Frontal gyrus	-0.114	-0.507	-0.190	0.000	0.280	0.522	0.387	0.374	0.444
Superior Frontal gyrus	1.141	1.199	1.128	1.762	1.787	1.088	0.387	0.224	0.868

Legend. Betweenness, Closeness, Strength indexes are reported. BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

4.3 Different patterns of white matter abnormalities and structural covariance in bipolar I and II disorders

Aims

The purpose of the current study was to analyze the fractional anisotropy (FA) data using univariate and multivariate approaches (SBM) to investigate regional covariance patterns of microstructural white matter changes in patients with BD-I and BD-II, compared to age- and sex-matched HCs. We also aimed to test the association between FA structural covariance and affective temperament ratings in such populations.

Based on previous research, we expected more pronounced alterations in white matter microstructure in patients with BD compared to controls, as well as a significant difference in FA between BD subtypes. In addition, we also hypothesized a significant correlation between FA structural covariance and affective temperament ratings in patients with BD.

Methods

Study Participants

Sixty patients with BD (30 BD-I and 30 BD-II) and 45 HC were enrolled for this study from the psychiatric ward and mood disorders service of the Padua University Hospital. The inclusion and exclusion criteria adhered to the parameters delineated in the first studies, ensuring consistency throughout the three presented studies.

Clinical assessment and temperament evaluation

In addition to the baseline clinical assessment (for a detailed description, see the dedicated chapter in the first study), each participant was also administered the Italian 35-item version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Scale (TEMPS-M) (Fico et al., 2020) to investigate the affective temperaments. The short version of the TEMPS-M consists of 35 items on a five-point Likert scale ranging from 1 to 5 (1 = “not at all”, up to 5 “very much”).

Five temperament scores (depressive, cyclotomic, hyperthymic, irritable, and anxious) measured by the TEMPS-M were entered into the statistical analysis of DTI data. As in the previous investigations, PEBL software (http://pebl.sourceforge.net/) was used to carry out all the computerized tests. A detailed mood disorder history, as well as current pharmacotherapy, including lithium serum levels and treatment duration, were gathered.

Image acquisition and Diffusion MRI preprocessing

High-resolution structural data were acquired using a 3T MR-scanner (3 Tesla Philips Ingenia) with a 32-channel quadrature head coil. Each participant underwent whole-brain 3D-T1 magnetization-prepared rapid gradient-echo sequence in the sagittal plane (see previous studies for a detailed description of parameters) and DTI echo-planar sequences with 48 noncollinear directions and b-value of 1000 s/mm2 (TE=91; TR=4513; FOV=224x224x140; axial scan plane, resolution=2.0x2.0x2.0mm3; number of sections=70).

DTI images were processed using FSL Software Library (http://www.fmrib.ox.ac.uk/fsl). Eddy correction tool was also implemented to correct for the gradient coil distortions and head motion artifacts. DTI fit was used to estimate the diffusion tensors, the diffusion direction, the mean diffusivity, and the FA value of each voxel (Behrens et al., 2003).

Source-based morphometry (SBM) and statistical analysis

The SBM analysis was conducted on preprocessed FA data. FA maps were smoothed using the Computational Anatomy Toolbox for SPM (CAT12) (http:// www.neuro.uni-jena.de/cat/), running within the Statistical Parametric Mapping analysis package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), with an 4 – 4 – 4 mm smoothing kernels (Caprihan et al., 2011). We applied the "minimum description length" criteria for component estimation (Li et al., 2007). ICA decomposition was performed using an Infomax algorithm within the "Group ICA for fMRI Toolbox" (GIFT, http://mialab.mrn. org/ software/gift). An ICASSO

algorithm (Himberg et al., 2004) that repeated the ICA procedure 100 times with both bootstrapping and permutation was also applied to increase the reliability of the estimate. After extracting the mixing matrix (IC loadings) for each subject, analysis where then computed through an ANOVA, with Bonferroni-corrected post-hoc for pairwise planned comparisons. Finally, to investigate the group differences in FA, we performed an ANOVA (FWE corrected) using SPM12.

Sociodemographic and clinical data were compared between groups using $\chi 2$-tests for categorical variables and one-way analyses of variance (ANOVA) for continuous variables, with pairwise chi-square/ Tukey post hoc comparisons in case of statistical significance.

To investigate the relationship between brain structure, clinical, and affective temperament ratings, we performed a Pearson's or Spearman's correlation between clinical data and the loadings for each IC appropriately. Data analysis was performed with the Jamovi (Version 1.2, https://www.jamovi.org) [Computer Software], and R (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL https://www.rstudio.com/.). The level of significance was set to $p<0.05$ for all tests.

Results

Demographic and clinical characteristics

Detailed demographic and clinical characteristics are presented in Table 6. We found no significant differences across BD-I, BD-II, and HC groups concerning age, sex, and IQ scores (all p's>0.05).

Table 6. Baseline characteristics of the study participants.

Characteristics	BD-I (N=30)	BD-II (N=30)	HC (N=45)	F/t or χ	p
Age (years), mean ± SD	44.233±12.974	39.533±12.431	41.511±13.130	1.021	0.366
Males, n (%)	21 (70)	19 (63.33)	26 (57.78)	1.156	0.561
IQ, mean ± SD	101.824±12.556	107.520±9.461	109.946±9.046	2.889	0.068

Legend. IQ, intelligence quotient; SD, standard deviation; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy controls.

BD subtypes did not differ in terms of age of onset, illness duration, familiarity for BD, the number of patients in current euthymic state, current lithium plasma levels, current HAM-D, MADRS, YMRS, and HAM-A scores (all p's>0.1). In comparison with patients with BD-II, those with BD-I displayed significantly lower GAF scores (p=0.003), a greater occurrence of past psychotic symptoms (p<0.001), lower use of antidepressants (p=0.001), greater use of antipsychotics (p=0.038), and a greater lifetime lithium exposure (p=0.033).

Affective Temperaments Ratings

The mean scores of depressive, cyclothymic, hyperthymic, irritable, and anxious temperaments are reported in Table 7. Notably, significant differences were observed among diagnostic subgroups in the TEMPS-M ratings of irritable (p=0.028) and hyperthymic temperaments (p=0.012). Patients with BD-I showed higher irritable temperament scores compared to HC (p=0.027), whereas ratings of irritable affective temperament did not differ significantly from those with BD-II and HC (p=0.976), and between BD subtypes (p=0.092).

Table 7. Differences of TEMPS-M temperament ratings across BD-I, BD-II, HC.

Variables	BD-I	BD-II	HC	F	p
TEMPS-M anxious, mean ± SD	12.6 (5.72)	11.9 (4.97)	11.8 (5.47)	0.117	0.890
TEMPS-M cyclothymic, mean ± SD	15.0 (8.21)	14.1 (5.44)	13.3 (6.75)	0.376	0.688
TEMPS-M depressive, mean ± SD	16.1 (5.38)	14.9 (6.01)	14.1 (5.55)	0.780	0.462
TEMPS-M hyperthymic, mean ± SD	19.1 (5.06)	17.3 (5.31)	21.9 (5.74)	4.75	0.012
TEMPS-M irritable, mean ± SD	15.2 (5.37)	12.1 (4.27)	11.8 (4.06)	3.75	0.028

Legend. TEMPS-M, the Italian 35-item version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Scale; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy control; SD, standard deviation.

DTI analysis, SBM analysis, and brain-behavior correlations

Compared with HC, patients with BD-I exhibited nine clusters of significant FA reduction spanning across the corpus callosum, the genu of the corpus callosum, the cingulum and parahippocampal circumvolution bilaterally, and parieto-occipital regions bilaterally (Figure 7a). Patients with BD-II also showed sixteen clusters of significant FA reduction encompassing the same anatomic structures when compared with HC (Figure 7b). Interestingly, patients with BD-II displayed two clusters of significantly greater FA located in the genu of the corpus callosum and in the right parahippocampal circumvolution relative to those with BD-I (Figure 7c).

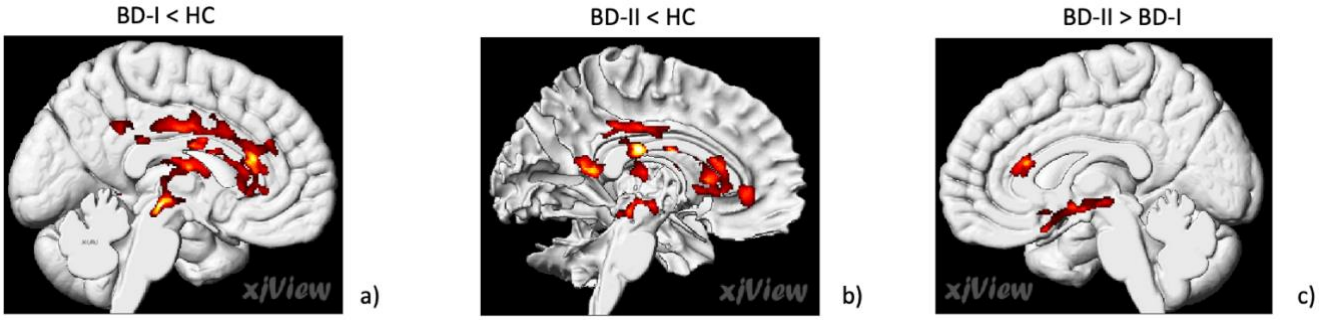

Figure 7. Clusters of significant differences in white matter FA values across BD-I, BD-II, and HC are displayed on a Montreal Neurological Institute template. FA, fractional anisotropy; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HC, healthy control.

For the SBM analysis, four main components were estimated. IC1 loadings showed a significant effect of diagnosis [$F(2,99) = 6.54$, $p = 0.002$], with planned comparisons revealing significant differences only between HC and BD-I ($p = 0.001$) (see Figure 8). IC3 loadings also showed a significant effect of diagnosis [$F(2,99) = 7.49$, $p < 0.001$] with planned comparison differences between HC and BD-II ($p = 0.019$) and between BD-II and BD-I ($p < 0.001$). Lastly, IC4 loadings revealed a significant effect of diagnosis [$F(2,99) = 7.65$, $p < 0.001$], with post-hoc tests showing significant differences between HC and BD-I ($p = 0.004$) and between HC and BD-II ($p = 0.005$).

Regarding the brain-behavior correlations, IC1 loadings had a significant positive correlation with the TEMPS-M irritable temperament ratings (rho=0.472, p = 0.048).

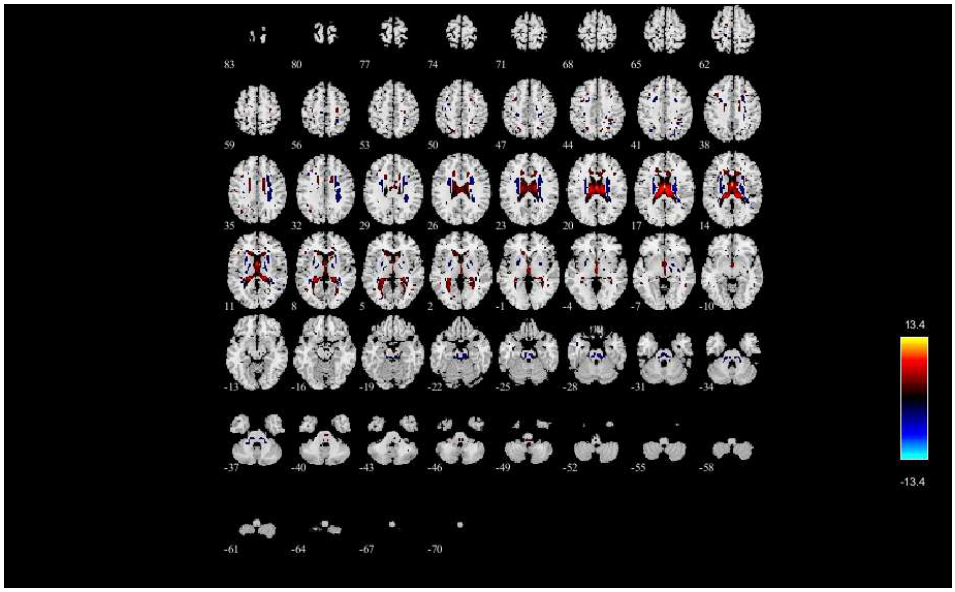

Figure 8. SBM component (IC1 loadings) encompassing cingolo-callosal-parahippocampal brain regions exhibited significantly lower white matter FA in patients with BD-I compared to HC, but not to the other groups. FA, fractional anisotropy; BD-I, bipolar disorder type I; HC, healthy controls.

5. Discussion

The current studies, which aimed to investigate the main BD subtypes using clinical, behavioral, and neuroimaging data analyzed with multivariate approaches, yielded several noteworthy findings.

The first study (Miola et al., 2022g) revealed that patients with BD-I exhibited decreased GMV in the insula, as well as in the temporal-occipital-parietal cortex, and the cerebellum compared with HC, with no significant differences between BD-II and HC nor between BD subtypes. In the brain regions with decreased GMV, those with BD-I displayed reduced structural covariance that was associated with a greater number of previous manic episodes, and worse executive functions, including visuospatial processing and problem-solving abilities. BD-I patients showed worse performance on FER than BD-II patients and this difference correlated with temporal-occipital GMV loss (Miola et al., 2022g).

Occipital-temporal regions have been implicated in face processing, particularly involving the fusiform region and the posterior-superior temporal sulcus (STS) as the core system of face processing (Haxby & Gobbini, 2007). Specifically, the fusiform has been implicated in the representation of invariant aspects of the face, whereas the posterior-STS has been involved in the representation of changeable aspects (e.g., facial expression) (Bernstein & Yovel, 2015). The ventral visual stream, extending from the occipital face area to the fusiform, has been found to be strongly influenced by emotional stimuli (Vuilleumier, 2005), with the amygdala having modulatory control over sensory processing at all stages of the ventral stream (Amaral et al., 2003). Therefore, in BD-I, lesser GMV in the STS and in the inferior occipital gyrus may be associated with impaired emotional processing, as also suggested by the association with FER performance.

Additionally, the prefrontal-temporal-occipital network with reduced structural network covariance in BD-I, encompasses the temporal-occipital regions that span the dorsal stream of visual processing. The dorsal stream originating from primary visual areas and reaching posterior

parietal areas has been involved in perceiving spatial information and guiding visuomotor 'actions'. Conversely, the ventral stream that originates from primary visual areas reaching the inferior temporal (ventral) region, has been implicated in object identification and its internal representation (Haxby et al., 1991; Ray et al., 2020). Consistently, the present findings unveiled an intriguing association between impaired executive functions, specifically related to visuospatial performance and problem-solving abilities (as exemplified by poorer performance in the TOH task) and the reduced structural network covariance associated with BD-I, but not BD-II or HC.

In summary, the study findings offer compelling evidence of structural abnormalities within the visual system of individuals with BD-I, aligning with observations in other psychotic disorders (Reavis et al., 2020). In line with the dynamic interplay and reciprocal interaction between emotional regulation and cognitive function (Lima et al., 2018), the present findings hint at the possibility that the altered structural covariance observed in the temporo-occipital network in BD-I may play a role in the intricate relationship between cognitive control and emotional processing, with altered structure resulting in dysfunctional integrative processing of mood and cognition.

The second study (Miola et al., 2023f) also revealed several noteworthy results. First, euthymic patients with BD-I displayed the poorest performance in FER, particularly for sadness processing. Second, in patients with BD-I, FER performance, specifically sadness-related FER performance, was negatively correlated with illness duration and with the number of previous manic episodes and positively associated with global functioning, as assessed with the GAF scale. Third, the overall structure of the network of BD subtypes was altered. Patients with BD-I showed a reduced GMV interrelationship in the frontal–insular–occipital regions. Furthermore, the edge strength between amygdala GMV and sadness-related FER performance was stronger in patients with BD-I compared to the other groups, as revealed by the edge invariance test. Finally, sadness-related FER performance was worse compared to neutral among those with BD-I and HC but not in patients with BD-II (Miola et al., 2023f).

Our findings of general FER performance impairment in BD are in line with previous reports (Rocca et al., 2009; Derntl & Habel, 2011; Hoertnagl et al., 2011; Soeiro-de-Souza et al., 2012; Ryan et al., 2013; David et al., 2014; Miola et al., 2022g) and have been found to be independent of visuoperceptual alterations (Bozikas et al., 2006). Of note, BD-I exhibited the poorest FER performance, particularly for sadness recognition, with a bias towards negative-valanced emotion being described during a mood episode but also in euthymic patients with BD-I, thus suggesting a trait-related impairment (Gopin et al., 2011; Sollier-Guillery et al., 2021). Furthermore, a previous study investigating FER performance in 36 patients with BD, 24 of their first-degree relatives, and 40 HC found poorer FER performance among the BD patients and their relatives compared with HC, suggesting FER performance as a candidate endophenotype in BD (Vierck et al., 2015). On the other hand, a sadness-related Facial Emotion Perception Test (FEPT) impairment has been found in clinically stable patients with BD, even when compared to those with MDD (Vederman et al., 2012). Interestingly, a recent evidence synthesis confirmed that patients with BD were less accurate than those with MDD in identifying each type of emotion (SMD = −0.24; 95%CI = −0.43, −0.05; p = 0.014), but these differences were more selective for sad faces (SMD = −0.31; 95%CI = −0.54, −0.08; p = 0.009) (De Prisco et al., 2023).

Regarding differences in emotion processing between patients with BD-I and BD-II, only a few reports specifically compared the BD subtypes (Bora, 2018), yielding controversial results. Some studies found no differences in FER performance between the BD subtypes (Summers et al., 2006; Martino et al., 2011; Jensen et al., 2021), while yet another small investigation suggested that euthymic patients with BD-II displayed better performance in fear recognition compared to manic or euthymic patients with BD-I (Lembke & Ketter, 2002). These conflicting findings might be attributed to methodological differences in investigating FER performance, including differences in facial stimulus standardization, facial expression dynamics variations, and performance assessment method discrepancies (Miskowiak et al., 2019).

Interestingly, we found that patients with BD-II had similar sadness-related and neutral-related FER performance compared to those with BD-I and HC. We hypothesized that the occurrence of more previous depressive episodes in patients with BD-II vs. BD-I, as emerged in our study, along with the more frequent depression-predominant polarity in patients with BD-II (Tondo et al., 2022a; Brancati et al., 2023), may result in greater familiarity in recognizing sadness in patients with BD-II. On the other hand, this finding could also be due to the better psychosocial functioning observed in patients with BD-II compared to those with BD-I, a pattern reported in our study but also previously (Dell'Osso et al., 2017).

Of note, the overall structure of the network of BD subtypes was significantly different compared with HC, as confirmed by the NCT. Specifically, the network plots of patients with BD-I revealed a reduced interrelationships among frontal–insular–occipital GMV ROIs implicated in emotional processing. These results partially align with a prior investigation utilizing a multivariate approach to study structural covariance (Sorella et al., 2019). That study identified two distinct structural networks: a shared psychotic core, encompassing portions of the medial parietal and temporal-occipital areas, along with parts of the middle frontal gyrus and cerebellum, which was equally reduced in patients with BD and SCZ compared to HC, and an affective core, more severely affected in patients with BD than those with SCZ, that spans across regions within the temporal and occipital lobes, frontal gyrus, and cerebellum (Sorella et al., 2019).

Additionally, the edge invariance test supported a stronger positive relationship between amygdala GMV and FER-sadness in patients with BD-I compared with HC, with no association of sadness-related FER performance with GMV in fronto-insular areas. Sadness-related FER processing in patients with BD-I appears to rely more on amygdala morphometry rather than frontal-insular-occipital areas. This underscores the potential significance of amygdala alterations as a crucial feature of BD (Blumberg et al., 2005; Kalmar et al., 2009). In BD-I, indeed, an altered cortico-limbic circuit may underlie disruptions in emotional processing (Bigot et al., 2020; Bi et

al., 2022; Mesbah et al., 2023), with patients with BD exhibiting hyperactivity in the amygdala and hippocampus and hypoactivation in the inferior frontal gyrus during emotion processing (Mesbah et al., 2023). In line with these findings, previous fMRI studies have shown reduced connectivity between the amygdala and the ventral prefrontal cortex, dorsolateral prefrontal cortex, and perigenual anterior cingulate cortex (Wang et al., 2009; Liu et al., 2014; Radaelli et al., 2015; Furlong et al., 2021). In summary, the present results align with a consensus model suggesting that BD-I is characterized by structural and functional abnormalities within critical emotional control networks, resulting in reduced connectivity, particularly between the ventral prefrontal cortex and limbic brain regions, notably the amygdala (Strakowski et al., 2012).

Of clinical relevance, the second study in the present series revealed that FER and sadness-related FER performance were worse in patients with BD-I with a higher number of manic episodes, a longer illness duration, and lower GAF scores. However, the available literature on this topic has yielded conflicting results. Some studies have failed to establish a clear association between FER performance and clinical variables (Martino et al., 2011; Işık Ulusoy et al., 2020), but others have suggested a detrimental effect of impaired emotion processing on psychosocial functioning even in currently euthymic patients with BD, in line with our findings (Lahera et al., 2012; Aparicio et al., 2017).

As reported above in the Methods and Results sections, patients with BD recruited for these studies were under pharmacological treatment at the time of the MRI scan. Nevertheless, no significant correlations between antipsychotic doses and IC loadings or with neuropsychological performance emerged in the first study (Miola et al., 2022g). Although the possibility that antidepressants can affect FER performance has been investigated in healthy volunteers (Harmer et al., 2003) and in patients with MDD (Tranter et al., 2009), the role of antidepressants on emotional processing in BD remains poorly understood. In this context, our second study revealed that sadness-related FER performance seemed to be independent of the use of antidepressants and

treatment with lithium. However, FER performance was negatively correlated with antipsychotic dose (Miola et al., 2023f).

Preliminary findings in the third study revealed that compared with HC, patients with BD-I and BD-II displayed nine and sixteen clusters of significant FA reduction, respectively, encompassing similar anatomic structures. These include the corpus callosum, the genu of the corpus callosum, the cingulum and parahippocampal circumvolution bilaterally, and parieto-occipital regions bilaterally. Of note, BD-II patients had two clusters of significantly greater FA located in the genu of the corpus callosum and in the right parahippocampal circumvolution when compared to those with BD-I.

Of the four components estimated using the SBM approach, IC1 loadings showed a significant effect of diagnosis, and planned comparisons suggested significant differences only between HC and BD-I, spanning the corpus callosum, the genu of the corpus callosum, the cingulum, and parahippocampal circumvolution bilaterally. In patients with BD-I, this SBM component of lower cingolo-callosal-parahippocampal FA covariance (IC1 loadings) had a significant positive correlation with the TEMPS-M irritable temperament score, which was significantly higher in patients with BD-I than in controls.

The third study aligns with a previous multicenter study from the ENIGMA-BD working group showing widespread white matter alterations in patients with BD compared to HC (Favre et al., 2019). Indeed, compared to HC, patients with BD displayed a significantly lower FA along multiple bundles, with the highest effect sizes observed within the corpus callosum and cingulum (Favre et al., 2019). Our findings are also in line with a previous systematic review (Duarte et al., 2016) and meta-analytic evidence of whole-brain DTI studies revealing lower FA in patients with BD near the parahippocampal gyrus, anterior and subgenual cingulate cortex (Vederine et al., 2011), as well as belongs right temporo-parietal junction and cingulum (Nortje et al., 2013).

Notably, only a few investigations have addressed possible FA differences between BD subtypes. In comparison to HC, both BD subgroups showed FA reductions in the white matter of

the corpus callosum, cingulum, and right prefrontal regions (Ha et al., 2011), as well as right thalamus and right subgenual anterior cingulate cortex (Liu et al., 2010). Compared to BD-I, BD-II had lower FA values in the right inferior longitudinal fasciculus (Ambrosi et al., 2016), in the right precuneus, right inferior frontal gyrus, and left inferior prefrontal area (Liu et al., 2010), whereas BD-I exhibited lower FA values in the right temporal white matter (Ha et al., 2011).

In addition, potential relationships between affective temperament ratings and white matter integrity using FA have not been systematically investigated to compare the main BD subtypes. Indeed, preliminary evidence found that affective temperaments are associated with white matter integrity in healthy subjects (Hatano et al., 2019), in healthy unaffected relatives of patients with BD (Sprooten et al., 2011), and in a group of mixed patients with major affective disorders (Serafini et al., 2011). The latter study investigating WMHs found that patients with mood disorders with higher dysthymia and lower hyperthymia displayed higher WMHs, mainly deep WMHs, along with greater hopelessness, higher suicidal risk, and more recent suicide attempts than those with higher hyperthymia and lower dysthymia (Serafini et al., 2011). Interestingly, a previous MRI investigation involving 117 healthy unaffected relatives of patients with BD and 79 HC found that unaffected relatives had reduced FA in one large widespread neuroanatomical cluster, including the corpus callosum, internal and external capsules, inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate fasciculi, parts of the corticospinal tract, and subcortical white matter around the central sulci, when compared with HC (Sprooten et al., 2011). Cyclothymic temperament rating was inversely related to FA in the internal capsules bilaterally and in left temporal white matter, regions also found to be reduced in subjects at high risk for BD. These findings provided evidence that white matter integrity can be considered an endophenotype for BD and suggest that impaired white matter integrity might be an underlying mechanism of genetic predisposition to BD (Sprooten et al., 2011).

In the third study of the present series, patients diagnosed with BD-I exhibited significantly higher TEMPS-M irritable temperament ratings compare to HC. However, irritable affective

temperament scores did not differ between those with BD-II and HC, nor between the BD subtypes. The highest irritable temperaments in those with BD-I are consistent with a recent report revealing that irritable temperament was a consistent predictor of both BD-I and BD-II, with a more prominent role in BD-I (Karam et al., 2023). Interestingly, the latter results were particularly robust since they resulted from multivariable regression analyses to control for the effect of other temperaments and taking into consideration relationships among all the five affective temperaments, with sex and age entered as covariates (Karam et al., 2023). Consistently, several other studies have found higher irritable temperament scores in patients with BD compared to those with MDD and, notably, even in comparison to HC (Evans et al., 2005; Nowakowska et al., 2005; Greenwood et al., 2013; Russo et al., 2014; Tondo et al., 2018). Again, in a previous report, multivariable logistic regression revealed that higher scores for dysthymic and anxious temperament were independently more likely among MDD than BD, whereas cyclothymic and irritable temperament scores were greater in BD than MDD (Miola et al., 2021). Of clinical relevance, irritable temperament scores were much greater in BD patients with co-occurring abuse of drugs or alcohol, as well as in subjects with suicidal acts, and significantly correlated with %-of-time during follow-up in mania or hypomania (Miola et al., 2021).

Of note, the work reported provides preliminary evidence of a significant positive correlation between TEMPS-M irritable temperament score and IC1 loadings in BD-I patients. In accord with a prospective, follow-up study (Miola et al., 2021), we hypothesize that the SBM component of lower cingulo-callosal-parahippocampal FA covariance (IC1 loadings) could represent a structural substrate of increased risk of substance abuse, suicidal behavior, and greater proportion of time spent in [hypo]mania in BD-I patients. However, these findings need further replication.

The current studies suffer from some limitations that need to be considered when interpreting the results. First, the cross-sectional study design limits the ability to draw firm conclusions and to make causal inferences about the relationship between abnormal structural connectivity and behavior. Second, the study did not include drug-free patients; for ethical and clinical reasons, it

would not be realistic to recruit drug-free patients, even when euthymic, to completely rule out the effects of the medication on neuropsychological and morphometric analysis. Pharmacological artifacts might have impaired cognitive performance and may have influenced neuroimaging measures. For example, lithium exposure may increase GMV, specifically in the limbic system and the amygdala (Savitz et al., 2010; Sani et al., 2018), whereas antipsychotic exposure has been associated with larger third ventricle, smaller hippocampus and supramarginal cortex volume (Abramovic et al., 2016). However, in this study, lithium exposure was similar between BD subtypes. Again, no significant correlations between antipsychotic doses, IC-loadings, and neuropsychological scores emerged in the first of the present studies. Conversely, sadness-related FER performance was negatively correlated with antipsychotic doses in the second investigation. Third, although most of the patients recruited were currently euthymic, we also included patients with depression at the time of evaluation in the first and third studies. Although most MRI investigations have reported on mixed groups of individuals with BD across various mood states assuming that mood state does not have a significant impact on brain structure, other studies have shown that the current mood state may affect brain structure (Brooks et al., 2009; Foland-Ross et al., 2012). Nevertheless, our findings were consistently replicated by a subgroup analysis limiting the sample to euthymic patients at the time of the scan to rule out a possible confounding effect of depression on GMV and structural covariance.

6. Conclusions

The reported studies have taken an integrated approach with clinical, behavioral, and morphometric data to seek evidence for a pattern of regions of GMV covariance loss in patients with BD, with the most substantial findings of differences between BD-I patients and controls. Of clinical relevance, abnormal prefrontal-temporal-occipital network in patients with BD-I was associated with greater illness severity and may reflect a neural signature associated with impairments in executive abilities, including visuospatial processing and problem-solving, as well as altered processing of emotions. Patients with BD-I displayed both general and selective impairment in FER, particularly for sadness recognition. Sadness-related FER impairment was associated with greater duration of illness, impaired daily functioning, and mood instability as expressed by a greater number of previous manic episodes. In addition, network analysis supports a model of fronto-limbic dysfunction in sadness processing in patients with BD-I relative to BD-II, in that BD-I showed evidence of a reduced GMV interrelationship in the frontal–insular–occipital regions and a greater edge strength between amygdala GMV and sadness-related FER performance compared with the other groups. Again, compared with HC, patients with both BD-I and BD-II showed significant FA reduction encompassing similar anatomic structures, including the corpus callosum, the cingulum and parahippocampal circumvolution bilaterally, and parieto-occipital regions bilaterally. Of note, patients with BD-I had two clusters of significantly lower FA localized to the genu of the corpus callosum and in the right parahippocampal circumvolution relative to those with BD-II. The SBM component of lower cingolo-callosal-parahippocampal FA covariance could represent a structural substrate of higher ratings for irritable temperament in patients with BD-I.

Using integrated approaches, incorporating clinical, behavioral, and neuroimaging data analysis, we also observed structural and behavioral differences between patients with BD-I and BD-II that support reported clinical and nosological differences between these BD subtypes. The

findings of altered structural networks in patients with BD may lead to more accurate prognosis prediction and more selective therapeutic interventions.

Future studies with a prospective longitudinal design are warranted to confirm the present findings and to address inferences about the causal directions of the relationships emerging between the pattern of abnormal structural network covariance, emotional processing, and affective temperaments in patients with BD. Moreover, it is essential to conduct additional longitudinal investigations to examine the impact of mood states and psychotropic treatments on FER performance, and to elucidate causal connections between emotional processing, daily functioning, and morbidity in patients with BD.

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