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Review article

Inflammation, anxiety, and stress in bipolar disorder and borderline personality disorder: A narrative review

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ABSTRACT

Bipolar disorder (BD) and borderline personality disorder (BPD) are serious and prevalent psychiatric diseases that share common phenomenological characteristics: symptoms (such as anxiety, affective lability or emotion dysregulation), neuroimaging features, risk factors and comorbidities. While several studies have focused on the link between stress and peripheral inflammation in other affective disorders such as anxiety or depression, fewer have explored this relationship in BD and BPD. This review reports on evidence showing an interplay between immune dysregulation, anxiety and stress, and how an altered acute neuroendocrine stress response may exist in these disorders. Moreover, we highlight limitations and confounding factors of these existing studies and discuss multidirectional hypotheses that either suggest inflammation or stress and anxiety as the *primum movens* in BD and BPD pathophysiology, or inflammation as a consequence of the pathophysiology of these diseases. Untangling these associations and implementing a transdiagnostic approach will have diagnostic, therapeutic and prognostic implications for BD and BPD patients.

1. Introduction

Bipolar disorders (BD) and borderline personality disorder (BPD) are serious and common psychiatric disorders. Their prevalence is difficult to estimate and varies across studies, but worldwide lifelong prevalence of BD spectrum has been measured at about 2.4 % (Merikangas et al., 2011), while around 2.7 % for BPD (Kienast et al., 2014). Arguably, these might be lifelong disorders with rising prevalence, for which pathophysiological insight and early treatment could greatly reduce the economic and health burdens on societies. These disorders exhibit common neuroimaging features, risk factors, comorbidities, phenomenological characteristics and symptoms (such as anxiety, affective lability or emotion dysregulation). Emotional dysregulation, also defined as affective instability, refers to brief mood fluctuations characterized by high intensity, temporal instability, and delayed recovery from dysphoria (Bayes et al., 2019). Furthermore, emerging studies of patients suffering from these disorders indicate similar alterations in neuroendocrine stress reactivity and inflammatory profiles, suggesting possible shared mechanisms that lead to immune dysregulation.

There is strong evidence that i) stress and anxiety are associated with immune dysregulation and inflammation, ii) inflammatory pathways are altered in some psychiatric disorders, and iii) stress and anxiety play an important role in emotion dysregulation disorders, such as BD and BPD. As discussed in Section 3, while stress may lead to anxiety, they are different entities, with stress being a state of pressure and tension in the individual, and anxiety more an "anticipation of a future threat" (Daviu et al., 2019).

This review will highlight the similarities of these two disorders in terms of symptomatology and behavioral traits, recall the relationships between stress, anxiety and inflammation, and how it is measured in psychiatric patients, and finally focus on the principal aim: to review the existing evidence on the relationship between immune dysregulation and stress in BD and BPD, and how acute stress may induce an altered inflammatory response in these disorders. Understanding their pathophysiology in terms of immune dysregulation and stress may help validate potential biomarkers to detect the severity of the disease and guide therapeutic interventions.

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2. Methods

To do so, we searched PubMed, Medline and Web Of Science databases for the keywords: (((Inflammation OR cytokines) AND (allostasis OR stress OR anxiety)) AND (affective dysregulation OR emotion dysregulation OR bipolar OR borderline)) and relevant articles (i.e. those concerning immune dysregulation in relation to stress in BD and BPD) were included. All articles that we reviewed were peer-reviewed, English-speaking, and published before January 2021. Due to the multifaceted nature of the research question, the inclusion criteria were non-systematic, and papers were included from the query results or from the references cited in the selected articles. All figures were prepared using BioRender.

3. Similarities between BD and BPD

BD and BPD are two mental disorders with high rates of mortality, severe functional impairment (Krahn, 2011; Leichsenring et al., 2011), and a high comorbidity of around 10 % in clinical settings (Zimmerman and Morgan, 2013). There are many similarities in terms of symptoms and neurological imaging findings between BD and BPD. Indeed, both disorders have been characterized as emotion dysregulation disorders. For instance, prominent theories on the etiology of BPD (Koenigsberg et al., 2002; Linehan, 1993) suggest that it is best described as an emotion dysregulation disorder caused by heightened emotional reactivity and an inability to regulate emotional responses, including coping with low-stress social situations. Concerning BD, hypersensitivity to emotional stimuli has been identified in euthymic BD patients, and increased emotional reactivity in manic ones, as compared to healthy controls (Henry et al., 2012). Furthermore, BD and BPD share early signs and symptoms (Chanen et al., 2016), such as impulsivity and affective instability or emotion dysregulation (Linhartová et al., 2019), sexual disinhibition, excessive spending, alcohol and drug misuse, and, sometimes, deliberate self-harm and suicidality (Bayes et al., 2019). Whether BD and BPD are independent or interdependent diseases is debatable to the point that BPD has been proposed as an 'ultra-rapid cycling' sub-type of BD due to the fluctuating mood symptoms observed in BPD patients (MacKinnon et al., 2006). However, important differences between BD and BPD can be found concerning treatment responses, inheritability, age of onset and illness course, and interpersonal difficulties that are present in BPD but not in BD (Sanches et al., 2019). Interestingly, anxiety is one of the most prevalent manifestations of both disorders (Benazzi, 2006; Henry et al., 2001; Kinrys et al., 2019). Some BPD reports have indicated a prevalence of any type of anxiety disorder as high as 89 %, which has the potential to diminish over time (Zanarini et al., 2004). Further, the prevalence of anxiety disorders is higher in BPD patients compared to patients with other personality disorders (Silverman et al., 2012). Similarly, anxiety disorders in BD may precede its onset (Caricasole et al., 2019) and it has been suggested that they may constitute an atypical presentation or a prodromal stage of BD (Du et al., 2017).

Furthermore, as discussed in Section 5, stress constitutes both a risk and aggravating factor for BD (Aas et al., 2016; Dienes et al., 2006; Grande et al., 2012; Kim et al., 2007; Post and Leverich, 2006; Sugaya et al., 2012) and BPD (Ball and Links, 2009; Lucas and Mcmichael, 2005), besides being associated with systemic inflammation (Heinz et al., 2003; Marsland et al., 2017; Slavish et al., 2015).

Finally, beyond behavioral characteristics, evidence from neuroimaging studies indicate that in both disorders brain emotional regulation networks are impaired. Abnormal connections between limbic regions (e.g. the amygdala) and the prefrontal cortex have been identified in BD (Chase and Phillips, 2017; Strakowski et al., 2012) as well as in BPD patients (Baczkowski et al., 2017). Similarly, lower brain glucose metabolism was measured in the brainstem, insula, and frontal white matter of both BPD and BD patients compared to healthy controls (Bøen et al., 2019). While there is some overlap in gray matter alterations between the two disorders, they can be significantly more diffused and marked in BD than in BPD (Rossi et al., 2013). However, a clear comparison of brain patterns between these two disorders is difficult to conduct due to the complexity and heterogeneity of studies and results (Baczkowski et al., 2017; Chase and Phillips, 2017; Houenou et al., 2011; Kanske et al., 2015). Thus, this topic will not be discussed further in this review.

4. Links between inflammation and stress or anxiety

Stress can be defined from different viewpoints, either by focusing on the stimulus or the response that results from this stimulus in an individual. One viewpoint may describe stress as an alteration of the normal physical and/or psychological homeostasis in response to external negative events that induce a state of pressure and tension in the individual, or "an emergency state of an organism in response to a challenge to its homeostasis" (Daviu et al., 2019). The negative events themselves are classed as the stress or stressors. A more dynamic definition may be that stress is "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her wellbeing" (Butler, 1993). For classification purposes, stress may include early life adversities, chronic stress, and acute stress. Responses to acute stress are often easier to evaluate experimentally and can be shaped by chronic or early life stress. For these reasons, this review will mainly focus on acute stress.

Stress has a distinct bidirectional interplay with anxiety, although they are different entities. Anxiety may be considered "the anticipation of a future threat" or "a temporally diffused emotional state caused by a potentially harmful situation, with the probability of occurrence of harm being low or uncertain" (Daviu et al., 2019). Stress may cause anxiety, but also primary anxiety can be considered a kind of stressor (Ray et al., 2017). The link between the two has a neurobiological basis since noradrenergic projections from the locus coeruleus to the basolateral amygdala can mediate acute-stress-dependent anxiety (Daviu et al., 2019).

In addition, both stress and anxiety have been increasingly associated with inflammation (Marsland et al., 2017). In fact, it has been repeatedly found that acute stress increases inflammatory markers (such as blood and salivary cytokines) in healthy subjects (Heinz et al., 2003; Marsland et al., 2017; Slavish et al., 2015). Similarly, it has been shown that chronic stress is associated with an increase in peripheral markers of inflammation (such as plasma IL-6) (Kiecolt-Glaser et al., 2003). Increased levels of peripheral cytokines have been found in models of anxiety disorders (interleukin[IL]-1 β, IL-6 and tumor necrosis factor-α [TNF-α]) (Grippo et al., 2005; Hodes et al., 2014), and in humans with mood and anxiety disorders (IL-1, IL-6, TNF-alpha, c-reactive protein [CRP]) (Dowlati et al., 2010; Howren et al., 2009). A recent metanalysis (Renna et al., 2018) showed that patients diagnosed with anxiety disorders, excluding any patient with a chronic physical illness, compared to healthy controls had moderately higher concentrations of pro-inflammatory markers (mainly IL1-β, TNF-alpha and IL6) in the blood, but no differences in anti-inflammatory cytokines, even when correcting for comorbid depression. This strongly suggests that patients with anxiety disorders have a dysregulation in immune responses. Through imaging studies, inflammation can also have an impact on connectivity in a variety of brain structures, and in particular on some regions associated with anxiety (e.g. anterior cingulate cortex, amygdala, insula) (Felger, 2018).

5. Measuring inflammation in psychiatric patients

Strong evidence links inflammation and immune dysregulation to some psychiatric disorders (Bellanti and Settipane, 2015; Dubois et al., 2018; Kramer et al., 2019; Lee et al., 2016; Nielsen et al., 2017; Wang et al., 2018; Yuan et al., 2019), but there is doubt as to the directional causality (Bauer and Teixeira, 2019). While the field of

immunopsychiatry is rapidly expanding, inflammation is not routinely measured in psychiatric patients in clinical settings. However, in research settings, markers of inflammation in psychiatry may be measured peripherally (e.g. in the plasma or in the saliva (Slavish et al., 2015)) or centrally (in post-mortem brain tissue or cerebrospinal fluid [CSF]) (Giridharan et al., 2020), and at rest or in relation to specific tasks.

A single blood or saliva test can be taken at rest to evaluate baseline levels of peripheral inflammatory markers and/or the state of hormonal systems which can influence the immune and inflammatory status (Kraynak et al., 2018), such as the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) system [for review, see (Eisenberger and Cole, 2012; Pavlov and Tracey, 2017)]. Peripheral inflammatory markers include, for example, pro-inflammatory (TNF-α, IL1, IL2, IL6, IL8, IL12, interferon-gamma, monocyte chemoattractant protein-1 [MCP1]) and anti-inflammatory (transforming growth factor-β [TGF-β], IL4, IL5, IL10, C-C motif chemokine ligand-14) cytokines and chemokines, their receptors (such as soluble TNF-receptor-1 [sTNF-R1]), blood immune cells, acute-phase proteins, antibodies and complement system components. However, it should be noted that measures of peripheral baseline levels of inflammatory markers are subject to a high intra- and inter-individual variability, notably due to environmental influences such as diet, smoking, obesity, circadian rhythm, autoimmune diseases and infections that can be directly or indirectly linked to the psychiatric disorder (Himmerich et al., 2019).

Alternatively, these markers can be evaluated before, during, and/or after a stressor, i.e. an activity or a situation that induces stress and/or anxiety in the subjects. Classic examples of psychosocial stressors include public speaking and mental arithmetic calculations, and are tested in the human experimental gold standard Trier Social Stress Test protocol (TSST) (Kirschbaum et al., 1993; Slavish et al., 2015). For example, arithmetical ability test and the TSST have been used to test cortisol response to acute stress in ADHD patients, compared to controls (Pesonen et al., 2011; Raz and Leykin, 2015).

Importantly, most of the inflammatory markers mentioned can also be measured in the CSF and brain tissue, which reflect the central inflammatory status. Questions remain about the relationship between peripheral and central inflammatory markers, their pathophysiological importance, and the possible directional causality. However, peripheral inflammatory markers are easier to obtain and have been shown in some cases to correlate with the central markers. For example, in major depressive disorder, plasma CRP strongly correlates with CSF CRP (Felger et al., 2018). Peripheral inflammatory markers have been more widely studied than central markers in psychiatric diseases, and this review will mainly focus on them to evaluate the associations between inflammation, stress and anxiety in BD and BPD.

6. Stress, anxiety and inflammation in BD and BPD

6.1. Stress, anxiety and inflammation in patients with BD

BD is characterized by alternating states of mania or hypomania, depression, sometimes mixed states, and phases of stable euthymic mood (American Psychiatric Association, 2013). As mentioned, stress and anxiety strongly impact BD states, and environmental stressors (e.g. childhood abuse or neglect, occupational and social adversities) can negatively impact both the course of the disease and its onset (Aas et al., 2016; Grande et al., 2012; Kim et al., 2007; Post and Leverich, 2006; Sugaya et al., 2012). In fact, patients exposed to early life stressors show earlier age of onset and their relapses are triggered by lower levels of stress, in agreement with a "sensitization" hypothesis (Dienes et al., 2006).

BD itself has been linked to increased levels of markers of peripheral inflammation (Hamdani et al., 2013; Wang et al., 2016), both as a state and a trait feature (Rowland et al., 2018; Misiak et al., 2020a). This is supported by the high co-occurrence of inflammatory and autoimmune disorders with BD (Hamdani et al., 2013), such as psoriasis, ulcerative colitis, rheumatoid arthritis (Charoenngam et al., 2019; Eaton et al., 2010) and diabetes (Cassidy et al., 1999). This association can also be seen in genetic studies that have shown that polymorphisms in the *TNF-α* and *IL1* genes are associated with BD-II and earlier onset age in BD patients, respectively (Czerski et al., 2008; Hamdani et al., 2013). Interestingly, antipsychotics and lithium can downregulate many inflammatory genes that have been found to be more commonly upregulated in monocytes from BD patients and offspring of BD patients compared to those from healthy controls (Knijff et al., 2007; Padmos et al., 2008).

In particular, inflammation can worsen with disease progression, with late-stage patients having higher peripheral pro-inflammatory cytokines (such as TNF-α) than early-stage ones when controlled for age (Kauer-Sant'Anna et al., 2009).

Recent cutting-edge findings on inflammation in BD comes from the study of trait- and state-related differences in gut microbiota composition and heterogeneity in BD compared to healthy controls (Sublette et al., 2021), which may either be the result or the effect of a dysimmunitary state in the disease.

Systematic reviews and meta-analyses show that CRP, IL6, sTNF-R1 and TNF-α are elevated in manic and depressive bipolar patients compared not only to healthy controls but also to euthymic bipolar patients (Goldsmith et al., 2016; Hamdani et al., 2013; Munkholm et al., 2013). In some cases, immune dysregulation normalized upon clinical remission of acute episodes (Langan and McDonald, 2009). A study on 66 manic and 40 depressive BD patients found higher white blood cell, neutrophil and monocyte count, as well as higher monocyte to lymphocyte and neutrophil to lymphocyte ratios in the manic compared to the depressive BD patients (Mazza et al., 2019). Irrespective of disease state, low-grade inflammation, as measured by high-sensitivity CRP, was associated with the diagnosis of BD in a retrospective health record-based study on 600 psychiatric patients (Osimo et al., 2018), and correlated with emotional hyper-reactivity and suicide attempts in 635 remitted BD patients (Dargél et al., 2018). Similarly, in 83 BD patients, serum IL6 and TNF-α baseline levels were higher than in 217 controls (Koga et al., 2019).

Hence, the presence of inflammation appears to be an important factor in BD. Using biomarkers in the prodromal phase of the disease (Brietzke et al., 2012) could help with diagnostic approaches, and might offer therapeutic options as well. Indeed, promising results of anti-inflammatory treatments in reducing BD symptoms, especially depressive ones, have been reported (Altinoz and Ozpinar, 2019; Husain et al., 2017; Rosenblat and McIntyre, 2017; Rosenblat et al., 2016). Further research on different levels of inflammation and its related mechanisms in each phase of BD is necessary (Modabbernia et al., 2013). An interesting question is thus how inflammatory and stress responses relate to stress and anxiety in BD (Fig. 1): the answer might offer pathophysiological, diagnostic and, perhaps, therapeutic insights.

One study directly assessed these aspects using acute stress responses to TSST in euthymic female patients with bipolar type I disorder (BD-I) and healthy controls. As summarized in Fig. 2, blunted acute responses to stress may exist in BD-I, as patients had a smaller increase in cortisolemia and heart rate following TSST, compared to controls (Wieck et al., 2013). At baseline, BD patients have a smaller proportion of Treg lymphocytes and more T cells, compared to healthy controls (do Prado et al., 2013; Wieck et al., 2013), and this difference is exacerbated after TSST, when BD patients show a further increase in activated T cells and an additional decrease in Treg, while stress triggers the opposite effects in healthy controls (Wieck et al., 2013). This coincides with the reduced cortisol secretion in response to stress in BD-I patients, indicating possible failure to control stress-dependent immune activation. This could be driven by altered nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) and mitogen-activated protein kinase (MAP-K) signaling that has been shown in patients' peripheral blood immune

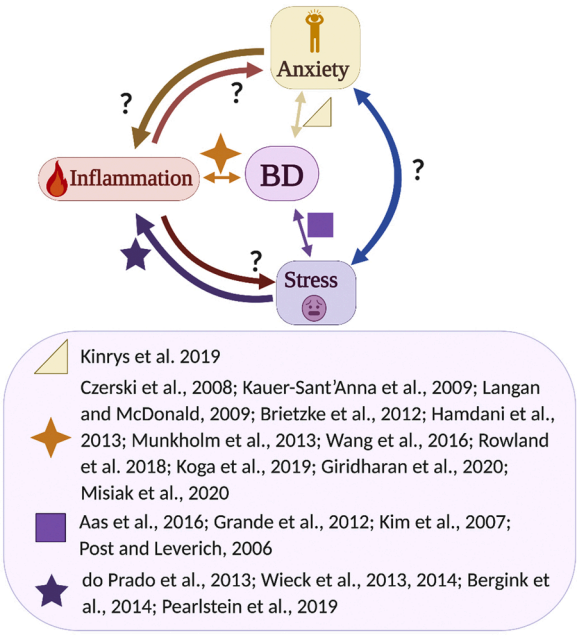

Fig. 1. Possible interplay between inflammation, stress and anxiety in bipolar disorder (BD). The diagram depicts hypothetical relationships (indicated by arrows) between inflammation, stress and anxiety in patients with BD. Arrows connect couples of variables specifying the putative direction of the association between them in BD patients. Shapes close to a certain color-matched arrow are associated with papers that support a link between the two specific variables connected by that arrow. Question marks indicate missing or insufficient evidence for a certain link.

cells (Bierhaus et al., 2003; Wieck et al., 2013). The same group (Wieck et al., 2014) continued to show that, in response to TSST, the magnitude of the pro-inflammatory cytokine IL2 increase in the blood was higher in BD-I patients than in controls, while sTNF-R1 (which is described to have inhibitory effects on TNF-α activity) decreased more in controls compared to patients. Additionally, although these are preliminary findings, a recent pilot study on 49 major depressive disorder and BD patients showed that TSST altered plasma IL6 and IL12 in all patients. Interestingly, increased psychobiological stress reactivity in IL12 and IL1β before cognitive behavioral therapy (CBT) predicted higher depressive symptoms following CBT (Pearlstein et al., 2019). Thus, psychobiological reactivity may be used to forecast symptom reduction outcome after CBT (Pearlstein et al., 2019). These studies strongly indicate that BD patients display inflammatory dysregulation and further research in this field could hold potential therapeutic options.

In summary, BD-I patients show altered neuroendocrine responses to stress (e.g reduced cortisol reactivity) (Fig. 2), which may lead to defective control of immune activation during stress (Table 1). These alterations may be due to a condition of allostasis and chronic stress (possibly also prenatal) in BD-I patients, which induce inflammation, leading to vulnerability to further stressors, increased anxiety, and "stress habituation" that decreases acute stress-dependent secretion of cortisol (Bergink et al., 2014; Grande et al., 2012; Kapczinski et al., 2008; Wieck et al., 2014). This condition may be exacerbated by the well-known sleep disturbances present in BD (Melo et al., 2016; Morris et al., 2018), since alterations in circadian rhythms have been associated both with higher morning cortisol (Vreeburg et al., 2009). This association is particularly relevant to stress and inflammation because the two have been linked to sleep disturbances (Dolsen et al., 2019; Irwin et al., 2016).

The reverse hypothesis may also be considered, in which BD pathophysiology leads to an inflammatory status that increases a patient's vulnerability to stress and anxiety, or to a higher likelihood of stress exposure, due to BD patients' impulsive behavior (Grandin et al., 2007). Interestingly, it has also been proposed that an altered gut microbiota may favor or induce HPA axis dysregulation, or vice versa (Misiak et al., 2020b). As mentioned, gut microbiota is altered in BD patients (Sublette et al., 2021).

The limitations to these preliminary studies are that some BD patients were on medications (e.g. lithium or valproate), which could interfere with intracellular signaling of acute stress response. Furthermore, some of these results are yet to be replicated in male patients (Wieck et al., 2014, 2013). This is particularly relevant as there is evidence of possible gender differences in inflammatory responses to stress (Lockwood et al., 2016; Prather et al., 2009).

6.2. *Stress, anxiety and inflammation in patients with BPD*

There is evidence for a causal link between stress and BPD (as reviewed by (Ball and Links, 2009)), as these authors argue that most of Hill's criteria for establishing a causal relationship are respected (see (Lucas and Mcmichael, 2005) for a review). In fact, childhood abuse, serious illnesses, and separation from parents have been repeatedly found to be more common in BPD than in other personality or psychiatric disorders, with a prevalence as high as 93 % (Golier et al., 2003; Laporte and Guttman, 1996; Oldham et al., 1996). Moreover, prospective studies have confirmed that these findings do not result from recall bias. Satisfying the dose-response criterion, abuse severity and duration correlate with some BPD symptoms, and there is epidemiological and biological plausibility (Rinne, 2013). For example, the fact that BPD is more common in females is in agreement with the higher prevalence of sexual abuse in this population (Finkelhor, 1994), and such life stressors have been associated with hippocampal atrophy in BPD (Sala et al., 2004). The specificity criterion is more difficult to prove, due to the multifactorial etiology of BPD: some patients do not report a history of childhood abuse, or victims of abuse may develop other kinds of psychiatric disorders, providing, however, some arguments for the analogy criterion (Ball and Links, 2009). Interestingly, stress is possibly related to symptoms of dissociation, a prominent component of BPD (Stiglmayr et al., 2008).

In line with the pivotal role of stressors in BPD etiology, many research groups reported an alteration in the HPA axis in BPD patients (Aleknaviciute et al., 2016; Bourvis et al., 2017; Duesenberg et al., 2019; Walter et al., 2008), similar to those seen in BD-I (Wieck et al., 2014). These studies have shown that in stressful conditions (e.g. a TSST), BPD patients show reduced cortisol responses and vagal (i.e. parasympathetic) activity (Weinberg et al., 2009) compared to healthy controls. Intriguingly, a study showed a negative correlation between the severity of early life stressors (i.e. the severity of hopelessness and physical neglect) and morning cortisol levels at rest in BPD patients (Mazer et al., 2019).

Possibly as a consequence of early life stressors and an impaired response to stress, anxiety symptoms, stress sensitivity and comorbidities are more common in BPD patients than in psychiatric outpatients without personality disorders and are positively associated with disease severity (Gratz et al., 2008; Quenneville et al., 2019).

Very few studies have investigated peripheral markers of inflammation in BPD (Fig. 3). Decreased antioxidant enzymes and IκBα levels (MacDowell et al., 2020), and increased inflammatory factors, such as COX2, iNOS, IL1β (Diaz-Marsa et al., 2012), and NFκB (MacDowell et al., 2020) were reported in plasma and peripheral blood mononuclear cells of BPD patients, compared to healthy controls. Interestingly, correlations with clinical symptoms were identified in some cases. In one of the aforementioned studies (MacDowell et al., 2020), NFκB and impulsivity scores were positively correlated. Similarly, plasma IL6 was shown to correlate with dissociation levels (Schmahl et al., 2013), and in BPD patients comorbid with major depression, increased vascular endothelial growth factor-1, serum cortisol, cortisol/DHEA ratios, TNF-αand IL6 have been found compared to controls (Kahl et al., 2006, 2009). Finally, it could be hypothesized that impaired vagal activity seen in some BPD

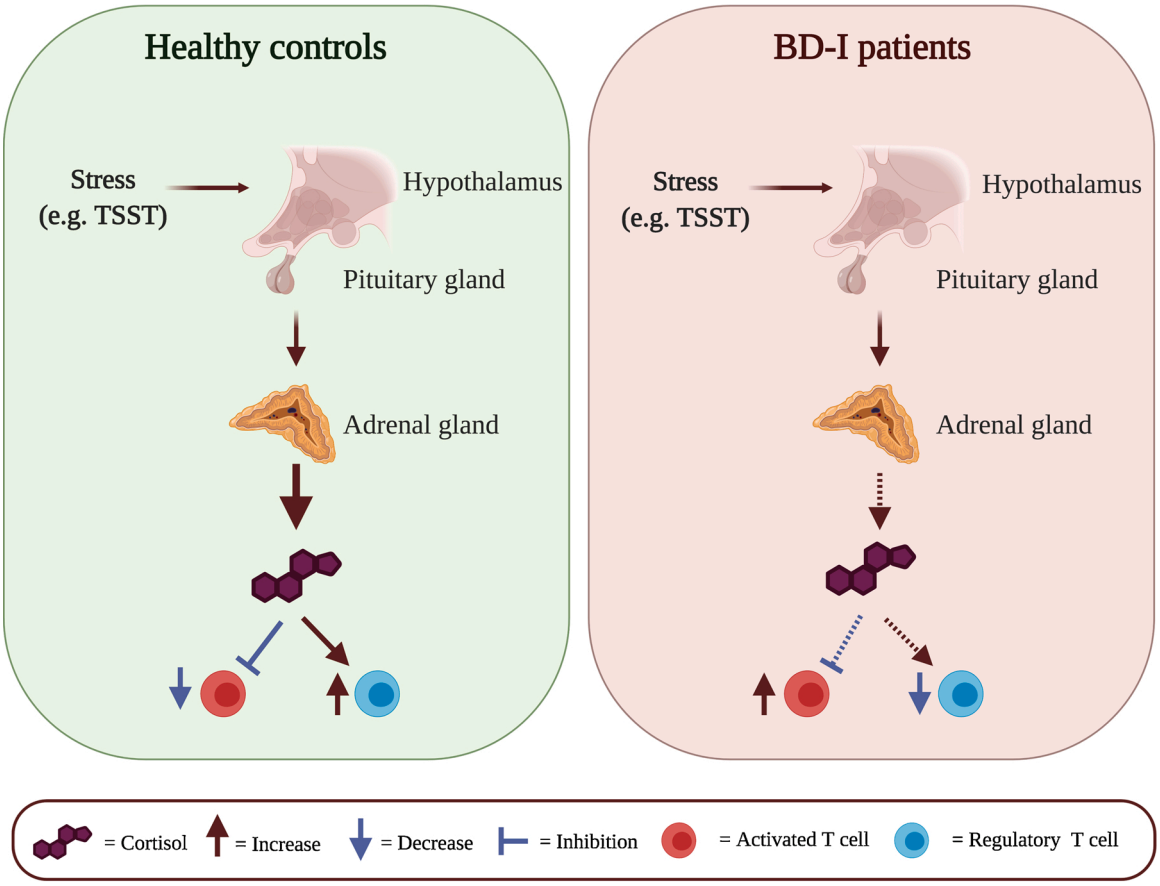

Fig. 2. Hypothalamic–pituitary–adrenal axis response to acute stress in bipolar type I disorder (BD-I) patients. Both in healthy controls and in patients suffering from BD-I, stressful stimuli (such as the Trier Social Stress Test protocol [TSST]), activate the hypothalamic–pituitary–adrenal (HPA) leading to cortisol secretion. However, cortisol secretion is reduced in BD-I compared to healthy controls. As a result, BD-I patients show a blunted cortisol-dependent immunomodulatory response to stressful stimuli, displaying more pro-inflammatory activated T cells (in red) and less anti-inflammatory regulatory T cell (blue) in their plasma, compared to healthy controls. Upward and red arrows represent increase and stimulation, respectively. Downward blue arrows signify decrease. Dashed lines signify weaker stimulation, as compared to solid ones.

patients (Weinberg et al., 2009) may contribute to inflammatory dysregulation. In fact, vagal nerve activation has been shown to regulate immune activation (Pavlov and Tracey, 2012), perhaps through the mediation of the noradrenergic nucleus locus coeruleus (Groves et al., 2005).

To our knowledge, no study has been conducted focusing on the precise effect of stress and anxiety on inflammation in BPD patients (Fig. 3). Thus, the field warrants further research to elucidate pathophysiological mechanisms and eventually identify biomarkers.

7. Conclusions

An intricate but fascinating network of connections between stress, inflammation, BD and BPD emerges from this review. Although many hypotheses and some experimental evidence exist on the topic, the directions and the implications of such connections are extremely open, and future research is needed to determine their precise interplay. Thus, the following and the aforementioned hypotheses are only speculative.

Hypothetically, emotion dysregulation disorders may expose an individual to stress, which, in turn, decreases the threshold for experiencing subjective stress, and leads to abnormal stress reactivity and inflammatory dysregulation. In contrast, stress reactivity may be the *primum movens* that predisposes individuals to emotion dysregulation disorders through the mediation of inflammation. Inflammation can affect brain structures, which might lead to a dysregulated stress response and, possibly, to emotion dysregulation disorders. Similarly, anxiety may be a mediator of the associations discussed above. Indeed, as described in the introduction, anxiety is associated both with an inflammatory response, and with BD and BPD. This possible confounder may be particularly challenging to address, since most existing studies on BD and BPD patients lack a systematic assessment of anxiety symptoms, which, additionally, may be mistaken for hypomanic ones (Perugi et al., 2001; Valença et al., 2005). As a matter of fact, anxiety may sometimes mimic a hypomanic episode due to an overlap in symptoms, such as sleep disturbances (e.g. sleep initiation troubles, without daily tiredness), concentration difficulties, irritability, restlessness, racing thoughts, and sometimes increased speech rate. Literature on the topic is sparse and therefore future studies should carefully assess psychopathological symptoms in addition to inflammatory state.

Finally, an unknown confounding variable may exist, which exposes individuals to a greater risk of BD or BPD and also of stress, inflammation, and/or emotion dysregulation disorders. Thus, the increased inflammatory status observed in emotion dysregulation disorders might be an effect, a cause or just an epiphenomenon of BD and BPD.

What needs to be considered is the fact that, as discussed above, anxiety is a common symptom in BD and BPD, possibly mediating this relationship. It has been associated with inflammatory dysregulation, and we could hypothesize that higher levels of anxiety imply greater sensitivity to stress, while also the opposite may be true (Ray et al., 2017). In fact, stress cortisol response correlates to anxiety levels in healthy individuals (Mujica-Parodi et al., 2014). Thus, an additional hypothesis may be that among all the models proposed in the previous

Table 1
Findings on the relationship between stress, anxiety and inflammation in BD. Principal findings concerning inflammatory alterations measured in BD patients in response or in relation to stress or anxiety are recapitulated in this table. BD, bipolar disorder; CBT, cognitive behavioral therapy; CRP, C-reactive protein; IL, interleukin; MAP-K, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TSST, Trier Social Stress Test; sTNF-R1, soluble TNF-receptor-1.

References (Study Type)	Findings
Dargél et al. (2018) (Cross-sectional study)	High levels of high-sensitivity CRP are associated with emotional hyper-reactivity and suicide attempts in 613 remitted BD patients
Wieck et al. (2013, 2014) (Cross-sectional studies)	In response to TSST: - BD patients show a blunted stress response - The ratio of Treg to activated T cells is decreased, compared to controls who show an increase of Treg/activated T cells. - BD patients show increased lymphocyte MAP-K p-ERK and p-NF-κB signaling after the stress challenge compared to control. - The magnitude of the pro-inflammatory cytokine IL2 increase in the blood is higher in BD-I patients than in controls, while anti-inflammatory sTNF-R1 decreases in a greater magnitude in controls than BD patients.
Pearlstein et al., 2019 (Longitudinal study)	TSST altered plasma IL6 and IL12 in 49 major depressive disorder and BD adolescents. Increased psychobiological stress reactivity in IL12 and IL1β before cognitive behavioral therapy (CBT) predicted higher depressive symptoms following CBT.

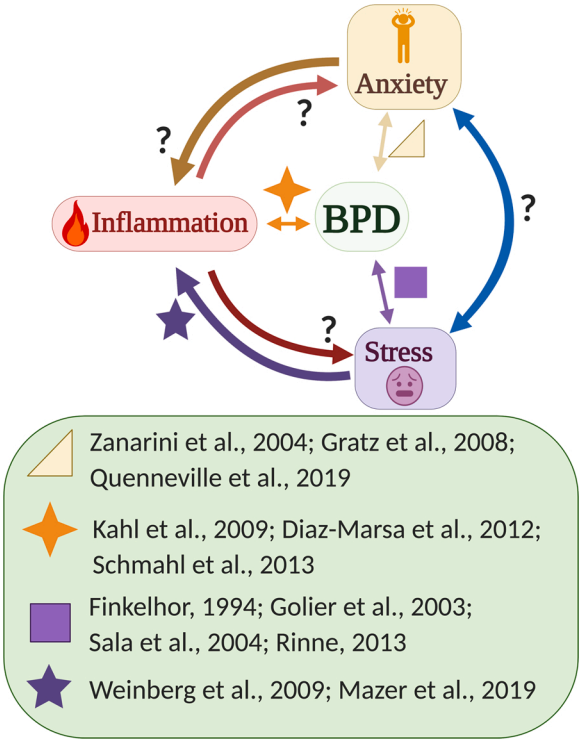

Fig. 3. Possible interplay between inflammation, stress and anxiety in borderline personality disorder (BPD). The diagram depicts hypothetical relationships (indicated by arrows) between inflammation, stress and anxiety in patients with borderline personality disorder (BPD). Arrows connect couples of variables specifying the putative direction of the association between them in BPD patients. Shapes close to a certain color-matched arrow are associated with papers that support a link between the two specific variables connected by that arrow. Question marks indicate missing or insufficient evidence for a certain link.

paragraph, the relationship between stress and inflammation may be modulated by anxiety. Anxiety might increase stress-dependent inflammation or exacerbate a possible role of inflammation in dysregulating stress response, as has already been shown in anxiety disorders (Dowlati et al., 2010; Howren et al., 2009; Renna et al., 2018). All these factors could also lead to an increased risk of developing emotion dysregulation disorders.

Whatever the mechanistic explanations underlying these relationships, their identification has important implications. Peripheral markers of inflammation and/or HPA axis dysregulation are easily assessed, especially in relation to stress and anxiety induced experimentally. Once they will be better defined, they may become part of screening tests for individuals at high-risk for BD or BPD, or markers of therapeutic response. Interestingly, these disorders do not only have in common their relation to stress, anxiety and inflammation, but they share many symptoms, risk factors, and are highly comorbid. Studies associating these disorders in the evaluation of the relationship between acute stress, anxiety and inflammation are thus extremely pertinent and may have quickly translatable clinical implications for diagnosis, prognosis, and in assessing treatment response in patients, or for risk evaluation in vulnerable individuals.

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Declaration of Competing Interest

The authors report no declarations of interest.

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